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(54) Title: MODULAR DESIGN AND SYNTHESIS OF AMINIMIDE CONTAINING MOLECULES

(57) Abstract

The design and synthesis of novel aminimide-derived molecular modules and the use of the modules in the construction of new molecules and fabricated materials is disclosed. The new molecules and fabricated materials are molecular recognition agents useful in the design and synthesis of drugs, and have applications in separations and materials science.

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MODULAR DESIGN AND SYNTHESIS OF AMINIMIDE CONTAINING MOLECULES

1. FIELD OF THE INVENTION

The present invention relates to the *logical* development of biochemical and biopharmaceutical agents and of new materials including fabricated materials such as fibers, beads, films, and gels. Specifically, the invention relates to the development of molecular modules based on aminimide and related structures, and to the use of these modules in the assembly of simple and complex molecules, polymers and fabricated materials with tailored properties; where said properties can be planned and are determined by the contributions of the individual building modules. The molecular modules of the invention are preferably chiral, and can be used to synthesize new compounds and fabricated materials which are able to recognize biological receptors, enzymes, genetic materials, and other chiral molecules, and are thus of great interest in the fields of biopharmaceuticals, separation and materials science.

2. BACKGROUND OF THE INVENTION

The discovery of new molecules has traditionally focused in two broad areas, biologically active molecules, which are used as drugs for the treatment of life-threatening diseases, and new materials, which are used in commercial, especially hightechnological applications. In both areas, the strategy used to discover new molecules has involved two basic operations: (i) a more or less random choice of a molecular candidate, prepared either via chemical synthesis or isolated from natural sources, and (ii) the testing of the molecular candidate for the property or properties of interest. This

discovery cycle is repeated indefinitely until a molecule possessing the desirable properties is located. In the majority of cases, the molecular types chosen for testing have belonged to rather narrowly defined chemical classes. For example, the discovery of new peptide hormones has involved work with peptides; the discovery of new therapeutic steroids has involved work with the steroid nucleus; the discovery of new surfaces to be used in the construction of computer chips or sensors has involved work with inorganic materials, etc. As a result, the discovery of new functional molecules, being ad hoc in nature and relying predominantly on serendipity, has been an extremely time-consuming, laborious, unpredictable, and costly enterprise.

A brief account of the strategies and tactics used in the discovery of new molecules is described below. The emphasis is on biologically interesting molecules; however, the technical problems encountered in the discovery of biologically active molecules as outlined here are also illustrative of the problems encountered in the discovery of molecules which can serve as new materials for high technological applications. Furthermore, as discussed below, these problems are also illustrative of the problems encountered in the development of fabricated materials for high technological applications.

2.1 Drug Design

Modern theories of biological activity state that biological activities, and therefore physiological states, are the result of molecular recognition events. For example, nucleotides can form complementary base pairs so that complementary single-stranded molecules hybridize resulting in double- or triple-helical structures that appear to be involved in regulation of gene expression. In another example, a biologically active molecule, referred to as a ligand, binds with another molecule, usually a macromolecule referred to as ligand-acceptor (e.g. , a receptor or an enzyme), and this binding elicits a chain of molecular events which ultimately

gives rise to a physiological state, e.g., normal cell growth and differentiation, abnormal cell growth leading to carcinogenesis, blood-pressure regulation, nerve-impulse-generation and -propagation, etc. The binding between ligand and ligand-acceptor is geometrically characteristic and extraordinarily specific, involving appropriate three-dimensional structural arrangements and chemical interactions.

2.1.1 Design and Synthesis of Nucleotides

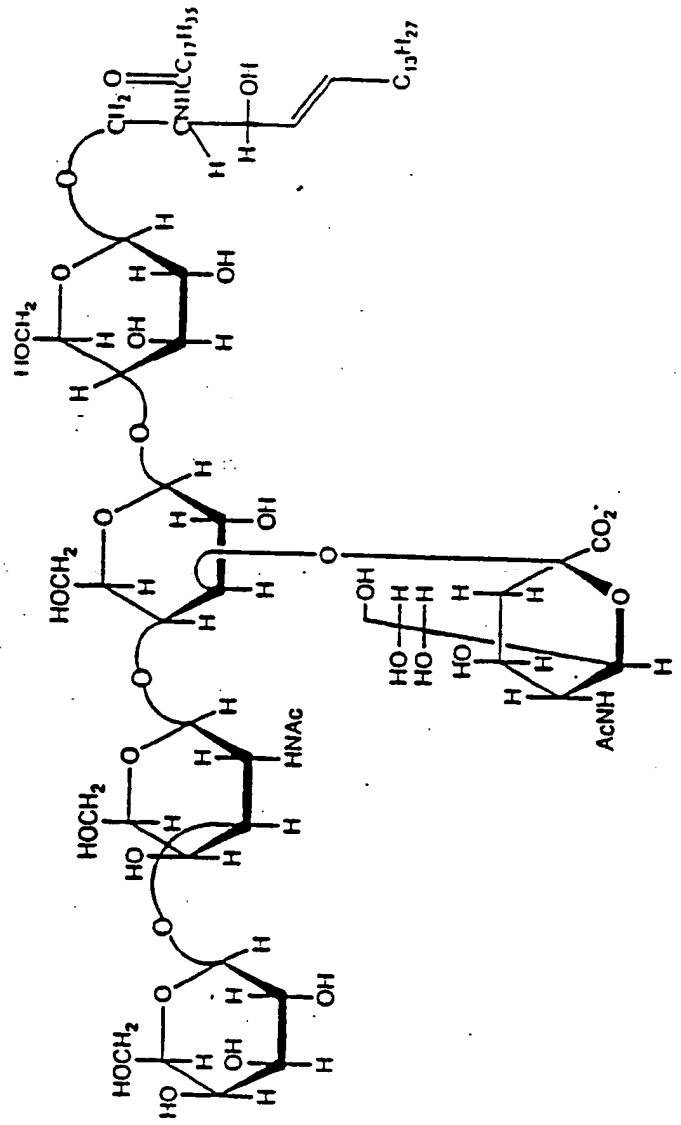
Recent interest in gene therapy and manipulation of gene expression has focused on the design of synthetic oligonucleotides that can be used to block or suppress gene expression via an antisense, ribozyme or triple helix mechanism. To this end, the sequence of the native target DNA or RNA molecule is characterized and standard methods are used to synthesize oligonucleotides representing the complement of the desired target sequence (see, S. Crooke, The FASEB Journal, Vol. 7, Apr. 1993, p. 533 and references cited therein). Attempts to design more stable forms of such oligonucleotides for use in vivo have typically involved the addition of various groups, e.g., halogens, azido, nitro, methyl, keto, etc. to various positions of the ribose or deoxyribose subunits (cf., The Organic Chemistry of Nucleic Acids, Y. Mizuno, Elsevier Science Publishers BV, Amsterdam, The Netherlands, 1987).

2.1.2 Glycopeptides

As a result of recent advances in biological carbohydrate chemistry, carbohydrates increasingly are being viewed as the components of living systems with the enormously complex structures required for the encoding of the massive amounts of information needed to orchestrate the processes of life, e.g., cellular recognition, immunity, embryonic development, carcinogenesis and cell-death. Thus, whereas two naturally occurring amino acids can be used by nature to convey 2 fundamental molecular messages, i.e., via formation

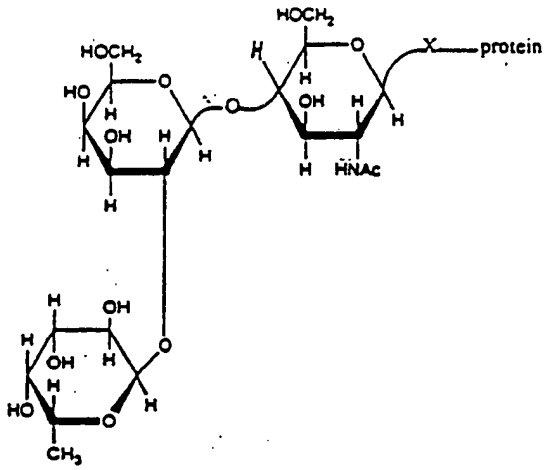
of the two possible dipeptide structures, and four different nucleotides convey 24 molecular messages, two different monosaccharide subunits can give rise to 11 unique disaccharides, and four dissimilar monosaccharides can give rise to up to 35,560 unique tetramers, each capable of functioning as a fundamental discreet molecular messenger in a given physiological system.

The gangliosides are examples of the versatility and effect with which organisms can use saccharide structures. These molecules are glycolipids (sugar-lipid composites) and as such are able to position themselves at strategic locations on the cell wall: their lipid component enables them to anchor in the hydrophobic interior of the cell wall, positioning their hydrophilic component in the aqueous extracellular milieu. Thus the gangliosides (like many other saccharides) have been chosen to act as cellular sentries: they are involved in both the inactivation of bacterial toxins and in contact inhibition, the latter being the complex and poorly understood process by which normal cells inhibit the growth of adjacent cells, a property lost in most tumor cells. The structure of ganglioside GM, a potent inhibitor of the toxin secreted by the cholera organism, featuring a branched complex pentameric structure is shown below.

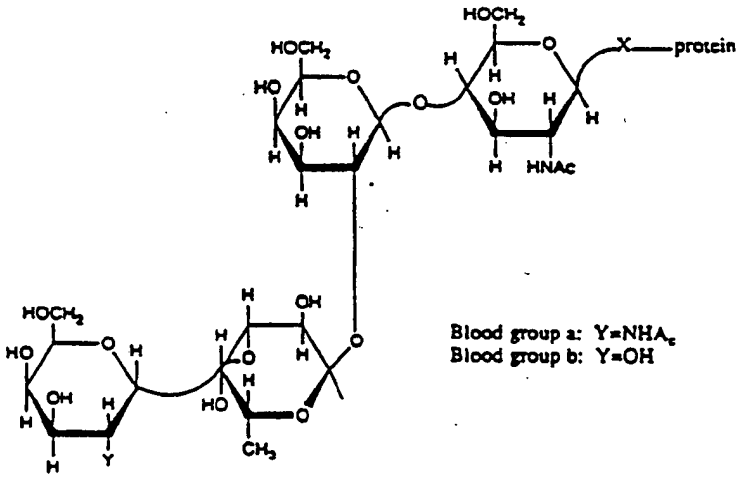


GANGLIOSIDE GM_1

The oligosaccharide components of the glycoproteins (sugar-protein composites) responsible for the human blood-group antigens (the A, B, and O blood classes) are shown below:



BLOOD GROUP O ANTIGEN, TYPE II



BLOOD GROUP A AND B ANTIGENS

Interactions involving complementary proteins and glycoproteins on red blood cells belonging to incompatible blood classes cause formation of aggregates, or clusters and are the cause for failed transfusions of human blood.

Numerous other biological processes and macromolecules are controlled by glycosylation (i.e., the covalent linking with sugars). Thus, deglycosylation of erythropoetin causes loss of the hormone's biological activity; deglycosylation of human gonadotropic hormone increases receptor binding but results in almost complete loss of biological activity (see Rademacher et al., Ann. Rev. Biochem 57, 785 (1988); and glycosylation of three sites in tissue plasminogen activating factor (TPA) produces a glycopolypeptide which is 30% more active than the polypeptide that has been glycosylated at two of the sites.

2.1.3 Design and Synthesis of Mimetics of Biological Ligands

A currently favored strategy for the development of agents which can be used to treat diseases involves the discovery of forms of ligands of biological receptors, enzymes, or related macromolecules, which mimic such ligands and either boost, i.e., agonize, or suppress, i.e., antagonize, the activity of the ligand. The discovery of such desirable ligand forms has traditionally been carried out either by random screening of molecules (produced through chemical synthesis or isolated from natural sources), or by using a so-called "rational" approach involving identification of a lead-structure, usually the structure of the native ligand, and optimization of its properties through numerous cycles of structural redesign and biological testing. Since most useful drugs have been discovered not through the "rational" approach but through the

screening of randomly chosen compounds, a hybrid approach to drug discovery has recently emerged which is based on the use of combinatorial chemistry to construct huge libraries of randomly-built chemical structures which are screened for specific biological activities. (S. Brenner and R.A. Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381)

Most lead-structures which have been used in "rational" drug design are native polypeptide ligands of receptors or enzymes. The majority of polypeptide ligands, especially the small ones, are relatively unstable in physiological fluids, due to the tendency of the peptide bond to undergo facile hydrolysis in acidic media or in the presence of peptidases. Thus, such ligands are decisively inferior in a pharmacokinetic sense to nonpeptidic compounds, and are not favored as drugs. An additional limitation of small peptides as drugs is their low affinity for ligand acceptors. This phenomenon is in sharp contrast to the affinity demonstrated by large, folded polypeptides, e.g., proteins, for specific acceptors, e.g., receptors or enzymes, which can be in the subnanomolar range. For peptides to become effective drugs, they must be transformed into nonpeptidic organic structures, i.e., peptide mimetics, which bind tightly, preferably in the nanomolar range, and can withstand the chemical and biochemical rigors of coexistence with biological tissues and fluids.

Despite numerous incremental advances in the art of peptidomimetic design, no general solution to the problem of converting a polypeptide-ligand structure to a peptidomimetic has been defined. At present, "rational" peptidomimetic design is done on an ad hoc basis. Using numerous redesign-synthesis-screening cycles, peptidic ligands belonging to a certain biochemical class have been converted by groups of organic chemists and pharmacologists to specific peptidomimetics; however, in the majority of cases the results in one biochemical area, e.g., peptidase inhibitor design using the enzyme substrate as a lead, cannot be transferred for use

in another area, e.g., tyrosine-kinase inhibitor design using the kinase substrate as a lead.

In many cases, the peptidomimetics that result from a peptide structural lead using the "rational" approach comprise unnatural alpha-amino acids. Many of these mimetics exhibit several of the troublesome features of native peptides (which also comprise alpha-amino acids) and are, thus, not favored for use as drugs. Recently, fundamental research on the use of nonpeptidic scaffolds, such as steroidal or sugar structures, to anchor specific receptor-binding groups in fixed geometric relationships have been described (see for example Hirschmann, R. et al., 1992 J. Am. Chem. Soc., 114:9699-9701; Hirschmann, R. et al., 1992 J. Am. Chem. Soc., 114:9217-9218); however, the success of this approach remains to be seen.

In an attempt to accelerate the identification of lead-structures, and also the identification of useful drug candidates through screening of randomly chosen compounds, researchers have developed automated methods for the generation of large combinatorial libraries of peptides and certain types of peptide mimetics, called "peptoids", which are screened for a desirable biological activity. For example, the method of H. M. Geysen, (1984 Proc. Natl. Acad. Sci. USA 81:3998) employs a modification of Merrifield peptide synthesis, wherein the C-terminal amino acid residues of the peptides to be synthesized are linked to solid-support particles shaped as polyethylene pins; these pins are treated individually or collectively in sequence to introduce additional amino-acid residues forming the desired peptides. The peptides are then screened for activity without removing them from the pins. Houghton, (1985, Proc. Natl. Acad. Sci. USA 82:5131; and U.S. Patent No. 4,631,211) utilizes individual polyethylene bags ("tea bags") containing C-terminal amino acids bound to a solid support. These are mixed and coupled with the requisite amino acids using solid phase synthesis techniques. The peptides produced are then recovered and

tested individually. Fodor et al., (1991, Science 251:767) described light-directed, spatially addressable parallel-peptide synthesis on a silicon wafer to generate large arrays of addressable peptides that can be directly tested for binding to biological targets. These workers have also developed recombinant DNA/genetic engineering methods for expressing huge peptide libraries on the surface of phages (Cwirla et al., 1990, Proc. Natl. Acad. Sci. USA 87:6378).

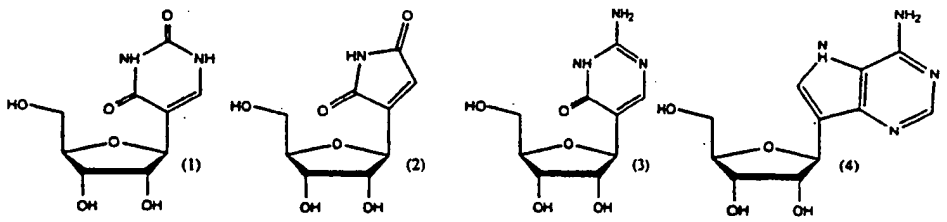
In another combinatorial approach, V. D. Huebner and D.V. Santi (U.S. Patent No. 5,182,366) utilized functionalized polystyrene beads divided into portions each of which was acylated with a desired amino acid; the bead portions were mixed together, then divided into portions each of which was re-subjected to acylation with a second desirable amino acid producing dipeptides, using the techniques of solid phase peptide synthesis. By using this synthetic scheme, exponentially increasing numbers of peptides were produced in uniform amounts which were then separately screened for a biological activity of interest.

Zuckerman et al., (1992, Int. J. Peptide Protein Res. 91:1) also have developed similar methods for the synthesis of peptide libraries and applied these methods to the automation of a modular synthetic chemistry for the production of libraries of N-alkyl glycine peptide derivatives, called "peptoids", which are screened for activity against a variety of biochemical targets. (See also, Symon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367). Encoded combinatorial chemical syntheses have been described recently (S. Brenner and R.A. Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381).

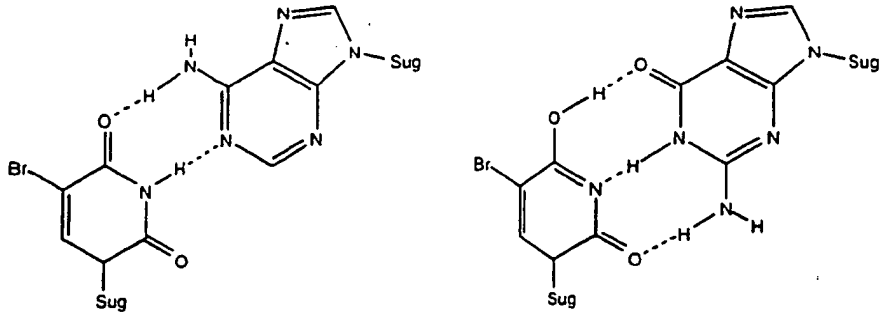
Recently in an alternate strategy for the design of therapeutically active mimetic ligands much attention has been focused on the construction and application of molecules which possess the property of binding to nucleic acids. These materials, whether they be direct Watson-Crick type "antisense" nucleotide mimetics, Hoogstein-type binders or minor groove binding compounds such as those pioneered by

Dervan and coworkers, have employed a variety of derivatives and variants of the naturally occuring sugar-phosphate backbone. Polyamide backbones have also been employed to support the base complements. While binding and desired functionality is observed *in vitro* withthese systems, they have inherent design drawbacks for *in vivo* use for hybridization against a rogue gene or its insidious RNA. The two main drawbacks of these polyamide systems are in (a) the persistent reliance upon an amide bond which is susceptible to proteolytic cleavage, and (b) the inability of the compound either as a class, or even singularly show efficient membrane permeability.

However, in the course of this work, a great amount of knowledge has been amassed *vis-a-vis* 1.) the ability of a synthetic scaffold to support a series of natural or designed bases in such a manner that tight binding to natural nucleic acids is observed; 2.) the requirements for designed or naturally occurring nucleotide bases other than guanosine, cytosine, thymidine, adenine, or uridine, to efficiently hydrogen bond (hybridize) to another, natural base or nucleotide. Among these natural nucleotide mimetics are showdomycin (1) and pseudouridine (2) and the synthetic compounds (3) and (4).



It has been demonstrated that such unnatural or modified bases can show efficient hybridization if projected from an effective scaffold as shown here for both tautomers of 5-bromouracil, which can bind to either adenine or guanine



The primary goal of any "antisense" or "gene therapy" is to inactivate the archival rogue information (deliterious DNA) or the messenger information (the correpsonding RNA) by very tight, specific hybridization.

As previously stated, there are a multitude of paths by which the "anti-sense" agent may be metabolized or destroyed outright, and as a result of these known obstacles, chemists have pursued alternative backbones that might enable their compounds to (a) survive the degradative response of the immune and metabolic pathways, and (b) transit the cellular and nuclear membranes to the site at which hybridization may occur.

In addition to the lead structure, a very useful source of information for the realization of the preferred "rational" drug discovery is the structure of the biological ligand acceptor which, often in conjunction with molecular modelling calculations, is used to simulate modes of binding of the ligand with its acceptor; information on the mode of binding is useful in optimizing the binding properties of the lead-structure. However, finding the structure of the ligand acceptor, or preferably the structure of a complex of the acceptor with a high affinity ligand, requires the isolation of the acceptor or complex in the pure, crystalline state, followed by x-ray crystallographic analysis. The isolation and purification of biological receptors, enzymes, and the polypeptide substrates thereof are time-consuming, laborious, and expensive. Success in this important area of biological

chemistry depends on the effective utilization of sophisticated separation technologies.

Crystallization can be valuable as a separation technique but in the majority of cases, especially in cases involving isolation of a biomolecule from a complex biological milieu, successful separation is chromatographic. Chromatographic separations are the result of reversible differential binding of the components of a mixture as the mixture moves on an active natural, synthetic, or semisynthetic surface; tight-binding components in the moving mixture leave the surface last en masse resulting in separation.

The development of substrates or supports to be used in separations has involved either the polymerization-crosslinking of monomeric molecules under various conditions to produce fabricated materials such as beads, gels, or films, or the chemical modification of various commercially available fabricated materials e.g., sulfonation of polystyrene beads, to produce the desired new materials. In the majority of cases, prior art support materials have been developed to perform specific separations or types of separations and are thus of limited utility. Many of these materials are incompatible with biological macromolecules, e.g., reverse-phase silica frequently used to perform high pressure liquid chromatography can denature hydrophobic proteins and other polypeptides. Furthermore, many supports are used under conditions which are not compatible with sensitive biomolecules, such as proteins, enzymes, glycoproteins, etc., which are readily denaturable and sensitive to extreme pH's. An additional difficulty with separations carried out using these supports is that the separation results are often support-batch dependent, i.e. they are irreproducible.

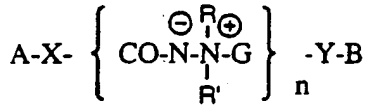
Recently a variety of coatings and composite-forming materials have been used to modify commercially available fabricated materials into articles with improved properties; however the success of this approach remains to be seen.

If a chromatographic support is equipped with molecules which bind specifically with a component of a complex mixture, that component will be separated from the mixture and may be released subsequently by changing the experimental conditions (e.g. , buffers, stringency, etc.) This type of separation is appropriately called "affinity chromatography" and remains an extremely effective and widely used separation technique. It is certainly much more selective than traditional chromatographic techniques, e.g chromatography on silica, alumina, silica or alumina coated with long-chain hydrocarbons, polysaccharide and other types of beads or gels which in order to attain their maximum separating efficiency need to be used under conditions that are damaging to biomolecules, e.g., conditions involving high pressure, use of organic solvents and other denaturing agents, etc.

The development of more powerful separation technologies depends significantly on breakthroughs in the field of materials science, specifically in the design and construction of materials that have the power to recognize specific molecular shapes under experimental conditions resembling those found in physiological media, i.e. , these experimental conditions must involve an aqueous medium whose temperature and pH are close to the physiological levels and which contains none of the agents known to damage or denature biomolecules. The construction of these "intelligent" materials frequently involves the introduction of small molecules capable of specifically recognizing others into existing materials, e.g. surfaces, films, gels, beads, etc., by a wide variety of chemical modifications; alternatively molecules capable of recognition are converted to monomers and used to create the "intelligent" materials through polymerization reactions.

3. SUMMARY OF THE INVENTION

A new approach to the construction of novel molecules is described. This approach involves the development of aminimide-based molecular building blocks, containing appropriate atoms and functional groups, which may be chiral and which are used in a modular assembly of molecules with tailored properties; each module contributing to the overall properties of the assembled molecule. The novel aminimide-derived molecules which are the subject of this invention have the following structure:



wherein:

a. A and B are the same or different, and each represents a chemical bond; hydrogen; an electrophillic group; a nucleophillic group; R; R'; an amino acid derivative; a nucleotide derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; and a macromolecular component, wherein A and B are optionally connected to each other or to other structures and R and R' are as defined below;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen, phosphorous, silicon or combinations thereof;

c. R and R' are the same or different and each represents A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R

and R', may be the same or different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

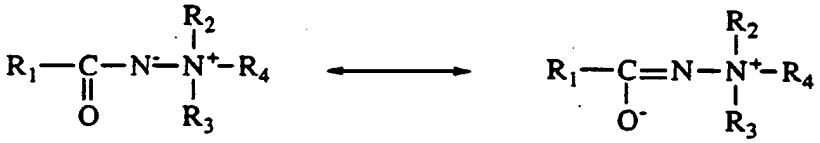
d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quarternary nitrogen and G may be different in adjacent n units; and

e. n is greater than or equal to 1;

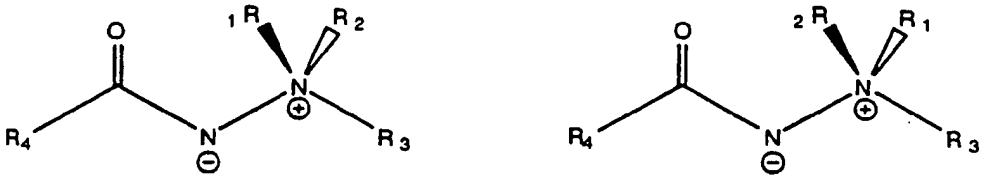
provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quarternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

3.1 Physical and Chemical Properties of the Aminimide Functional Group

Aminimides are zwitterionic structures described by the resonance hybrid of the two energetically comparable Lewis structures shown below:

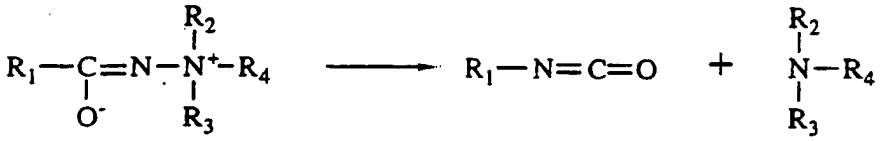


The tetrasubstituted nitrogen of the aminimide group can be asymetric rendering aminimides chiral as shown by the two enantiomers below:



As a result of the polarity of their structures, but lack of net charge, simple aminimides are freely soluble in both water and (especially) organic solvents.

Dilute aqueous solutions of aminimides are neutral and of very low conductivity; the conjugate acids of simple aminimides are weakly acidic, pKa of ca. 4.5. A striking property of aminimides is their hydrolytic stability, under acidic, basic, or enzymatic conditions. For example, boiling trimethyl amine benzamide in 6 N NaOH for 24 hrs leaves the aminimide unchanged. Upon thermolytic treatment, at temperatures exceeding 180_C, aminimides decompose to give isocyanates as follows.



The aminimide building blocks of the invention can be used to synthesize novel molecules designed to mimic the three-dimensional structure and function of native ligands, and/or interact with the binding sites of a native receptor. This logical approach to molecular construction is applicable to the synthesis of all types of molecules, including but not limited to mimetics of peptides, proteins, oligonucleotides, carbohydrates, lipids, polymers and to fabricated materials useful in materials science. It is analogous to the modular construction of a mechanical device that performs a specific operation wherein each module performs a specific task contributing to the overall operation of the device.

The invention is based, in part, on the following insights of the discoverer. (1) All ligands share a single universal architectural feature: they consist of a scaffold structure, made e.g., of amide, carbon-carbon, or phosphodiester bonds which support several functional groups

in a precise and relatively rigid geometric arrangement. (2) Binding modes between ligands and receptors share a single universal feature as well: they all involve attractive interactions between complementary structural elements, e.g., charge- and pi-type interactions, hydrophobic and Van der Waals forces, hydrogen bonds. (3) A continuum of fabricated materials exists spanning a dimensional range from 100 Angstroms to 1 cm in diameter, comprising various materials of varied construction, geometries, morphologies and functions, all of which possess the common feature of a functional surface which is presented to a biologically active molecule or a mixture of molecules to achieve recognition between the molecule (or the desired molecule in a mixture) and the surface. And (4) Aminimide structures, which have remained relatively unexplored in the design and synthesis of biologically active compounds and especially of drugs, would be ideal building blocks for constructing backbones or scaffolds bearing the appropriate functional groups, that either mimic desired ligands and/or interact with appropriate receptor binding sites; furthermore, aminimide modules may be utilized in a variety of ways across the continuum of fabricated materials described above to produce new materials capable of specific molecular recognition. These aminimide building blocks may be chirally pure and can be used to synthesize molecules that mimic a number of biologically active molecules, including but not limited to peptides, proteins, oligonucleotides, polynucleotides, carbohydrates, lipids, and a variety of polymers and fabricated materials that are useful as new materials, including but not limited to solid supports useful in column chromatography, catalysts, solid phase immunoassays, drug delivery vehicles, films, and "intelligent" materials designed for use in selective separations of various components of complex mixtures.

Examples describing the use of aminimide-based modules in the modular assembly of a variety of molecular structures are given. The molecular structures include

functionalized silica surfaces useful in the optical resolution of racemic mixtures; peptide mimetics which inhibit human elastase, protein-kinase, and the HIV protease; polymers formed via free-radical or condensation polymerization of aminimide-containing monomers; and lipid-mimetics useful in the detection, isolation, and purification of a variety of receptors. Accordingly, the present invention relates to a novel class of aminimide compounds and their use in the construction of simple and complex molecules and macromolecular combinations of molecules.

The present invention also relates to the use of said aminimide compounds in biochemical and biopharmaceutical applications as well as their use in materials such as fibers, beads, films and gels.

The present invention also relates to the use of the inventive class of compounds to logically develop intelligent molecules and fabricated materials which are able to recognize biological receptors, enzymes, genetic materials and chiral molecules.

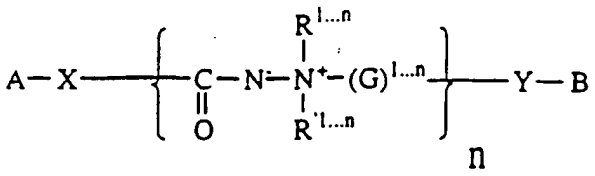
Still further, the present invention relates to the synthesis of libraries of aminimide-based molecules employing techniques herein disclosed or other techniques well known to those skilled in the art.

In addition, the present invention relates to chirally pure compounds, that may be synthesized chirally pure and can be used to recognize other chiral compounds.

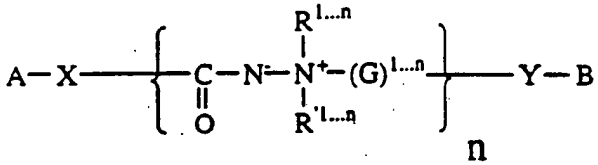
Yet still further, the present invention relates to a class of aminimide compounds that can be used as mimetics for numerous biologically active agents.

The present invention also relates to aminimide molecules which posess enhanced hydrolytic and enzymatic stabilities, and in the case of biologically active materials, are transported to target ligand-acceptor macromolecules in vivo without causing serious side effects.

The invention is also directed to a method of making a polymer having a particular water solubility comprising the steps of; a) choosing a first monomer having the formula



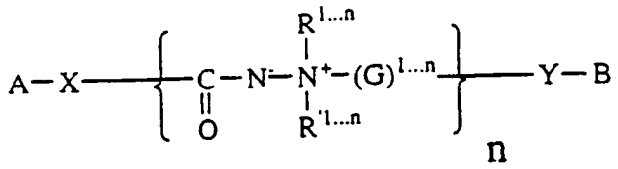
wherein R and R' are the same or different and are chosen from those organic moieties exhibiting hydrophobicity; b) choosing a second monomer having the formula



wherein R and R' are the same or different and are chosen from those organic moieties exhibiting hydrophilicity; and c) reacting said monomers to provide an effective amount of each monomer in a developing polymer chain until a polymer having the desired water solubility is created. According to this method said hydrophobic organic moieties can include those which do not have carboxyl, amino or ester functionality. Also said hydrophilic moieties can include those which do have carboxyl, amino or ester functionality.

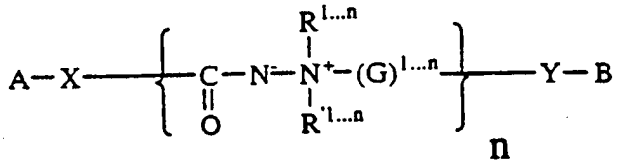
This invention is further directed to using said method of preparing a synthetic compound to produce a compound that mimics or complements the structure of a biologically active compound of the formula. This method can be used to produce pharmacaphores, peptide mimetics, nucleotide mimetics, carbohydrate mimetics, and reporter compounds, for example.

This invention is also further directed to a method of preparing a combinatorial library which comprises: a) preparing a compound having the formula;



$n \geq 1$; and b) conducting further reactions with the compound to form a combinatorial library.

Still further this invention is directed to a method of separating a desired compound from a plurality of compounds, which comprises; a) preparing a separator compound having the formula:



$n \geq 1$;

b) contacting said separator compound with the plurality of compounds; and c) differentiating said second compound and the separated compounded from said plurality of compounds.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1.1 Use of the Aminimide Group as a Mimetic of the Amide Group

The aminimide group mimics several key structural features of the amide group, such as overall geometry (e.g., both functional groups contain a planar carbonyl unit and a tetrahedral atom linked to the acylated nitrogen) and aspects of charge distribution (e.g., both functional groups contain a carbonyl with significant negative charge development on the oxygen). These structural relationships can be seen below, where the resonance hybrids of the two groups are drawn.

Being hydrolytically and enzymatically more stable than amides and possessing novel solubility properties due to their zwitterionic structures, aminimides are valuable building blocks for the construction of mimetics of biologically active molecules with superior pharmacological properties. For the purposes of this invention the term biological activity is defined as having a beneficial biological effect. For the construction of these mimetics, the aminimide backbone is used as a scaffold for the geometrically precise attachment of structural units possessing desired stereochemical and electronic features, such as suitable chiral atoms, hydrogen-bonding centers, hydrophobic and charged groups, pi-systems,

etc. Furthermore, multiple aminimide units can be linked in a variety of modes, using likers of diverse structures, to produce polymers of a great variety of structures. Specific molecular forms are chosen for screening and further study using several criteria. In one instance, a certain aminimide structure is chosen because it is novel and has never been tested for activity as a biopharmaceutical agent or as material for device construction. In a preferable instance, an aminimide ligand is chosen because it incorporates structural features and properties suggested by a certain biochemical mechanism. In another preferable case, the aminimide structure is the result of assembly of molecular modules each making a specific desirable contribution to the overall properties of the aminimide-containing molecule.

Summarizing, aminimides are functional groups with unusual and very desirable physiochemical properties, which can be used as molecular modules for the construction of molecular structures that are useful as biopharmaceutical agents and as new materials for high technological applications.

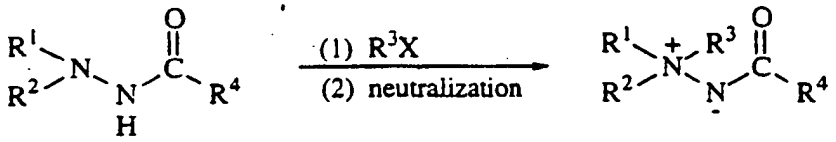
4.2 General Synthetic Routes to Aminimides

Aminimides can be synthesized in a variety of different ways. The compounds of the present invention can be synthesized by many routes. It is well known in the art of organic synthesis that many different synthetic protocols can be used to prepare a given compound. Different routes can involve more or less expensive reagents, easier or more difficult separation or purification procedures, straightforward or cumbersome scale-up, and higher or lower yield. The skilled synthetic organic chemist knows well how to balance the competing characteristics of competing strategies. Thus, the compounds of the present invention are not limited by the choice of synthetic strategy and any synthetic strategy that yields the compounds described above can be used.

The scope of this invention is intended to encompass each species of the aforementioned Markush genus. Thus, for example, where there is a numeric designation in the claim, that can be an integer, i.e. m or n, the scope of this invention is intended to cover each species that would be represented by every different integer.

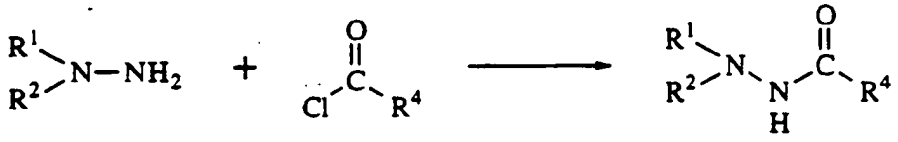
4.2.1 Aminimides via Alkylation of N,N-Disubstituted Hydrazides

Alkylation of a hydrazide followed by neutralization with a base produces an aminimide



This alkylation is carried out in a suitable solvent, such as a hydroxylic solvent, e.g., water, ethanol, isopropanol or a dipolar aprotic solvent, e.g., DMF, DMSO, acetonitrile, usually with heating. An example of this reaction is the synthesis of the trifluoroacyl-analide dipeptide elastase inhibitor mimetics shown in the examples below.

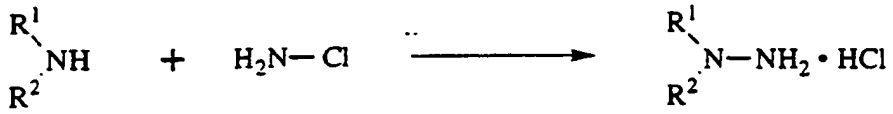
The hydrazide to be used in the above synthesis is produced by the reaction of a 1,1-disubstituted hydrazine with an activated acyl derivative or an isocyanate, in a suitable organic solvent, e.g., methylene chloride, toluene, ether, etc. in the presence of a base such as triethylamine to neutralize the haloacid generated during the acylation. This reaction is represented as follows:



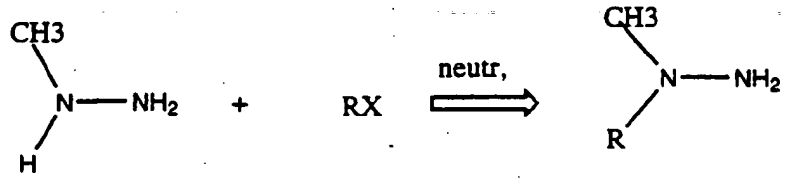
Activated acyl derivatives include acid chlorides, chlorocarbonates, chlorothiocarbonates, etc.; the acyl derivative may also be replaced with a suitable carboxylic acid and a condensing agent such as N,N-dicyclohexylcarbodiimide (DCC).

The alkylating agent R^3X used in the hydrazide alkylation may be an alkyl halide (X = Cl, Br, I), a tosylate (X = OTs), or some other suitable reactive species, such as an epoxide.

The desired 1,1-disubstituted hydrazines may be readily prepared in a number of ways well known in the art: for example, the reaction of a secondary amine with NH_2Cl in an inert organic solvent.



A second synthetic route for the preparation of hydrazines is alkylation of monoalkyl hydrazines, shown below for methyl hydrazine:



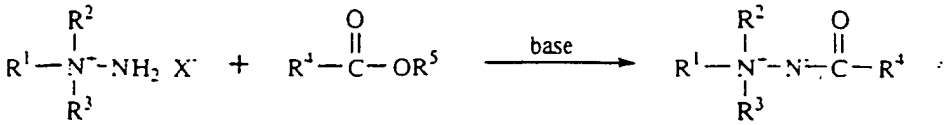
Detailed experimentals for the synthesis of a number of 1,1-disubstituted hydrazines via this reaction are set forth in the examples below.

The above route to aminimides is broadly applicable and allows the incorporation of a wide variety of aliphatic, aromatic and heterocyclic groups into various positions in the aminimide structure.

4.2.2 Aminimides via Acylation of 1,1,1-Trialkyl Hydrazinium Salts

Acylation of a suitable trialkyl hydrazinium salt by an acyl derivative or isocyanate in the presence of a strong

base in a suitable organic solvent, e.g. dioxane, ether, acetonitrile, etc. produces good yields of aminimides.

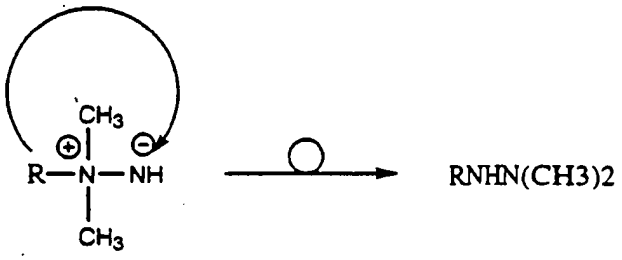


The acyl derivatives for the acylation reaction are the same as those required for the synthesis of the hydrazides outlined above.

This hydrazinium salt synthesis method can be subject to the possibility of rearrangements and side reactions which compete with the formation of the aminimide. The conditions under which these rearrangements can take place are highly dependent on the specific substituents on the quarternary nitrogen and, thus, the application of this synthetic route for the production of aminamide-derived species needs to take into consideration the specific nature of the desired R groups at this position.

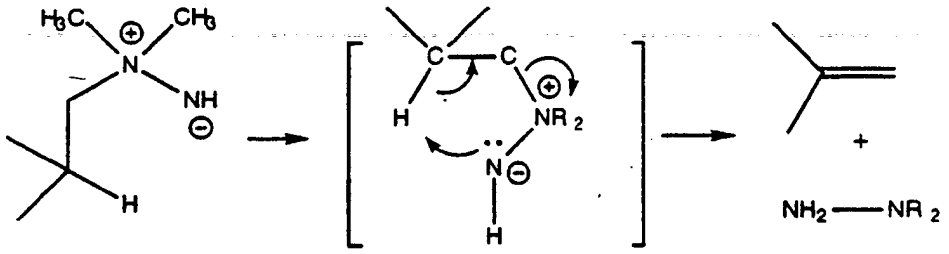
Two basic rearrangements are possible:

a. Migration of a substituent group from the quaternary nitrogen to form a hydrazide (Wawazoneck rearrangement - cf. Chem. Rev., 73, 255, 1972; Ind. Eng. Chem. Prod. Res. Devel., 19, 338, 1980).



The facility of this rearrangement is highly dependent on the nature of the substituent group. Alkyl and aryl substituents, as well as substituents attached to the quaternary nitrogen with alkyl or aryl connecting groups require vigorous reaction conditions, while allylic substituents migrate under much milder conditions. Thus, 1-benzyl-1,1-dimethyl hydrazinium chloride requires heating with powdered potassium hydroxide at 200-300^{0}C to effect rearrangement to the hydrazide, while 1-allyl-1,1-dimethyl hydrazinium chloride rearranges in 1M aqueous sodium hydroxide in 3 hours at 60^{0}C (Chem. Ber., 103, 2052, 1970) and 1,1-dimethyl-1-phenacyl hydrazinium bromide has been reported to rearrange in n-propanol at reflux (Tetrahedron Lett., 38, 3336, 1977)

b. Elimination reaction with substituents posessing a beta hydrogen:

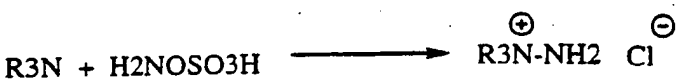


This reaction has been postulated to be responsible for the generation of cyclohexene from dimethylcyclohexyl hydrazinium chloride and a mixture of butene isomers from dimethyl s-butyl hydrazinium chloride on refluxing the hydrazinium salts with potassium t-butoxide in refluxing t-butanol (J. Org. Chem., 39, 1588, 1974).

While these rearrangements do not present any fundamental problem in the syntheses which are the subject of the present invention, they must be kept in mind in selecting synthetic strategies and reaction conditions for the assembly of ligands via hydrazinium intermediates bearing substituent groups which may be subject to these competing side-reactions.

In some cases, it may be appropriate to select other synthetic pathways for a specific assembly step involving such a module. Alternatively, the reaction may be carried out using mild reaction conditions to avoid any rearrangement.

The required hydrazinium salts may be prepared by routine alkylation of a 1,1-disubstituted hydrazines or by treatment of a tertiary amine with a haloamine (see 78 J. Am. Chem. Soc. 1211 (1956)). Alternatively, a tertiary amine may be reacted with hydroxylamine-O-sulfonic acid (prepared by the method of Goesl and Meuwsen; Chem. Ber., 92, 2521, 1959), as shown:

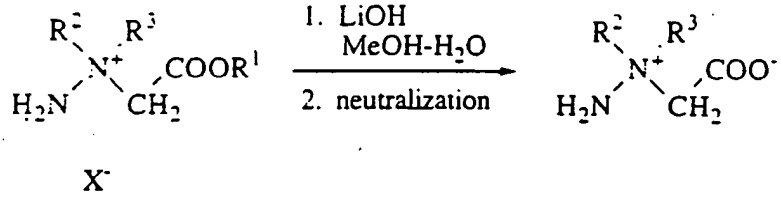


This reaction is carried out by reacting a suspension of the tertiary amine in a vigorously stirred cold aqueous solution of an equivalent amount of potassium carbonate sesquihydrate, containing a small amount of EDTA, with a cold solution of an equivalent amount of hydroxylamine-O-sulfonic acid in water, added over a 1 hour period. Methanol is added, and the precipitated K2SO4 is removed by filtration. The filtrate is adjusted to pH 7 with hydrochloric acid and the solvent is removed on a rotary evaporator. The hydrazinium salt is isolated by precipitation from the thick glassy residue by the addition of acetone.

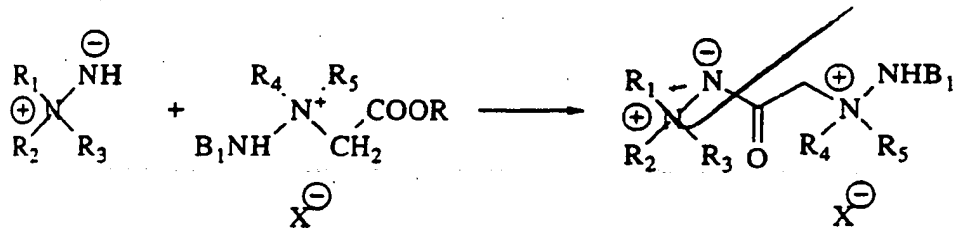
Hydrazinium salts, being chiral at nitrogen, may be resolved, e.g. , by treatment with a chiral acid followed by separation of the diastereomers (e.g., using chromatography or fractional crystallization and the resulting enantiomers used in stereoselective syntheses of aminimides.

When one of the alkyl groups in a hydrazinium salt is an ester group, the ester may be saponified efficiently using LiOH in a mixture of methanol and water, producing a useful -

hydrazinium acid after neutralization of the reaction mixture with an acid.

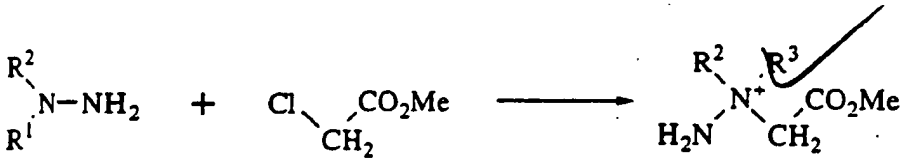


Suitably protected hydrazinium carboxylates may be used in condensation reactions to produce aminimides. Procedures analogous to those known to be useful in effecting peptide bond formation are expected to be useful; e.g. DCC or other carbodiimides may be used as condensing agents in solvents such as DMF.

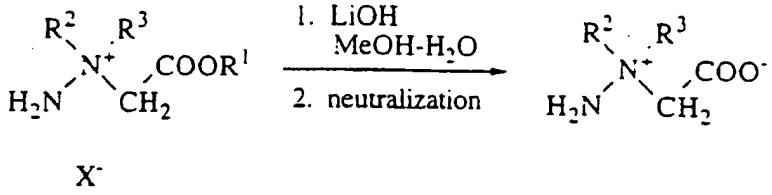


Alternatively, the hydrazinium carboxylate units may be coupled with alpha-amino-acids or with other nucleophiles, such as amines, thiols, alcohols, etc., using standard techniques, to produce molecules of wide utility as ligand mimetics and new materials for high technological applications.

The alpha-hydrazinium esters may, in turn, be produced by the alkylation of a 1,1-disubstituted hydrazine with a haloester under standard reaction conditions, such as those given above for the alkylation of hydrazides.



hydrazinium acid after neutralization of the reaction mixture with an acid.



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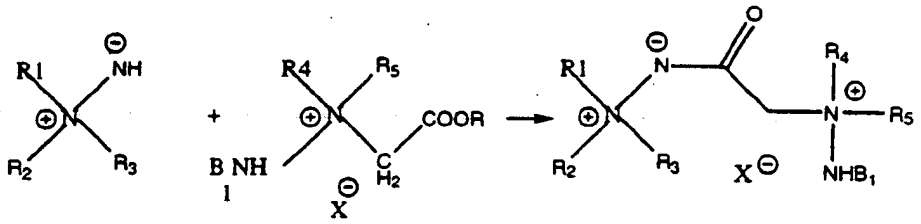

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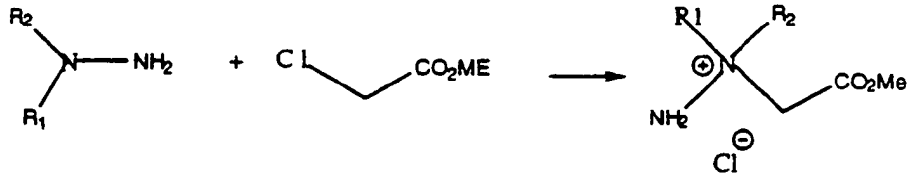
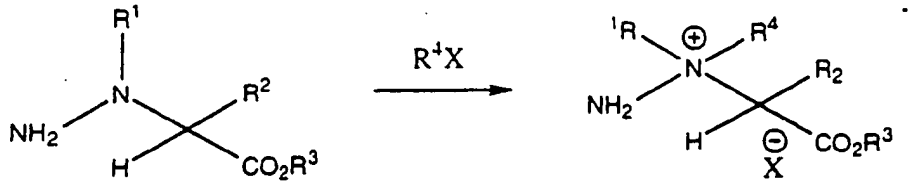
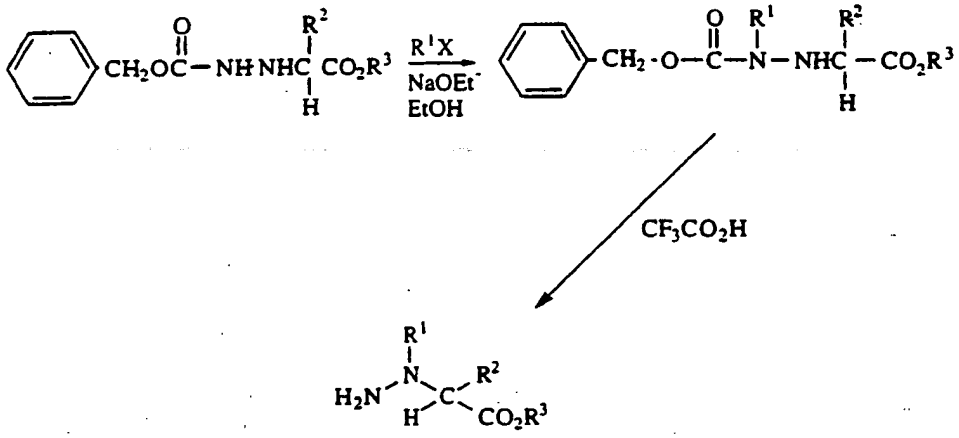


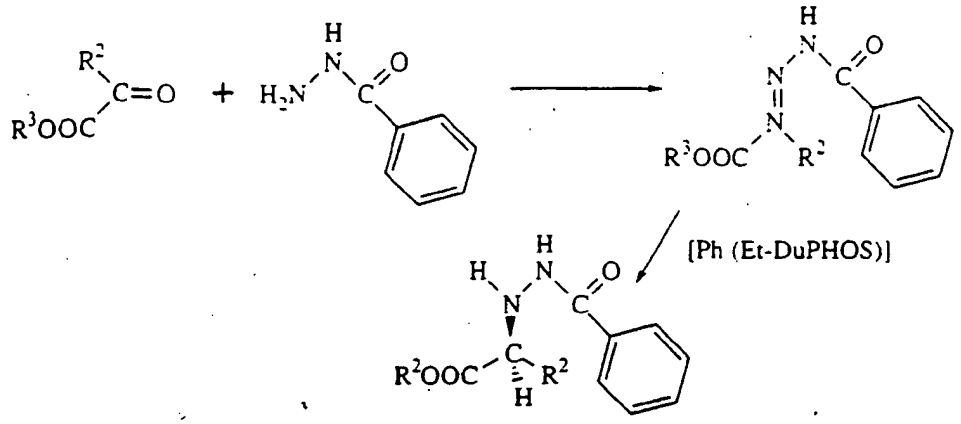
Alternatively, these hydrazinium esters may be produced by standard alkylation of the appropriate alpha-hydrazino ester.



The required 1,1-disubstituted hydrazine for the above reaction may be obtained by acid or base hydrolysis of the corresponding hydrazone (see 108 J. Am. Chem. Soc. 6394 (1986)); the alkylated hydrazone is produced from the monosubstituted hydrazide by the method of Hinman and Flores (24 J. Org. Chem. 660 (1958)).



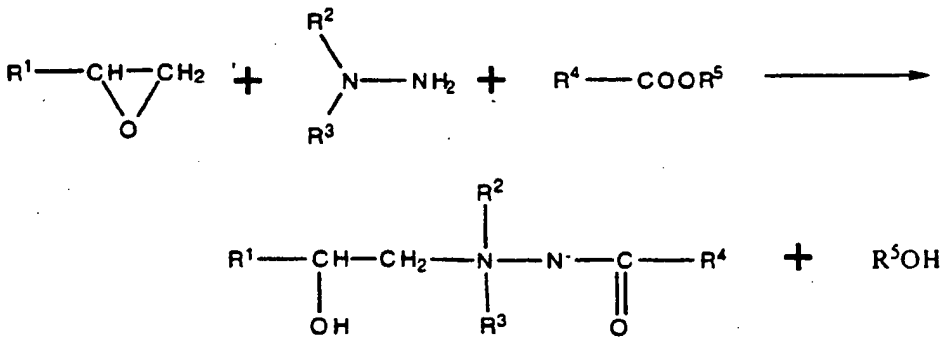
The monosubstituted hydrazided required above may be obtained by reduction of the Schiff base formed from an alpha-keto ester and a suitable hydrazide. This reduction may also be carried out stereoselectively, if desired, using DuPHOS-Rhodium catalysis (114 J. Am. Chem. Soc. 6266 (1992); 259 Science 479 (1993)), as shown:



In a variation of the synthesis given above, omega-halo aminimides are prepared using an omega-halo acyl halide (prepared by acylation of the trisubstituted hydrazinium tosylate salt with a haloalkyl acyl halide, such as ClCH2COCl) These halo aminimides may be reacted with nucleophiles containing reactive hydroxyl, thio, or amino groups to give aminimide derivatized molecules.

4.2.3 Aminimides via the Hydrazine-Epoxide-Ester Reaction

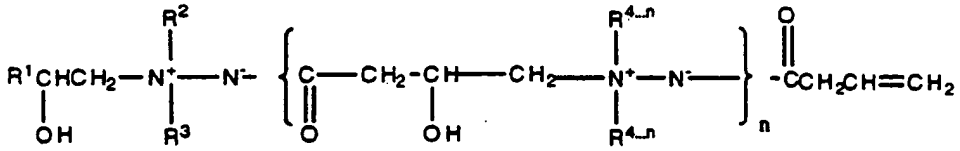
A very useful and versatile synthesis of aminimides involves the one-pot reaction of an epoxide, an asymetrically disubstituted hydrazine, and an ester in a hydroxylic solvent. usually water or an alcohol, which is allowed to proceed usually at room temperature over several hours to several days.



In the equation above, R1, R2 and R3 are selected from a set of diverse structural types (e.g. alkyl, carbocyclic, aryl, aralkyl, alkaryl or many substituted versions thereof), and R4 and R5 are alkyl, , carbocyclic, cycloalkyl, aryl or alkaryl.

The rates for the above reaction increase with increasing electrophilicity of the ester component. Generally, a mixture of 0.1 mol of each of the reactants in 50-100 ml of an appropriate solvent is stirred for the required period at room temperature (the reaction may be monitored by thin layer chromatography). At the end of this period, the solvent is removed in vacuo to give the crude product.

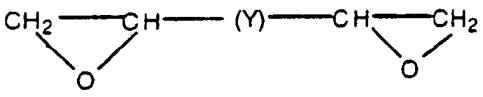
If substituent R4 of the ester component in the above aminimide formation contains a double bond, an aminimide with a terminal double bond results which may be epoxidized, e.g. using a peracid under standard reaction conditions, and the resulting epoxide used as starting material for a new aminimide formation. Thus, a structure containing two aminimide subunits results. If the aminimide-formation and epoxidation sequence is repeated n times, a structure containing n aminimide subunits results; thus when R4 is propene, n repetition of the sequence results in the structure shown below:



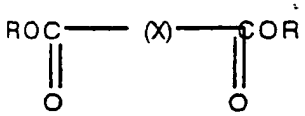
where the designations R2 and R3 are used to illustrate the manner in which the hydrazine substituents R2 and R3 can be varied in each polymerization step to produce oligomers or polymers of diverse structures. This is described in examples which follow below.

A related aminimide polymerization sequence utilizes an ester moiety bonded directly to the epoxide group.

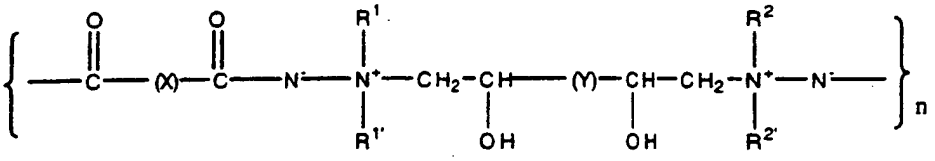
An additional related polymerization sequence involves the use of bifunctional epoxides and esters of the following form



and



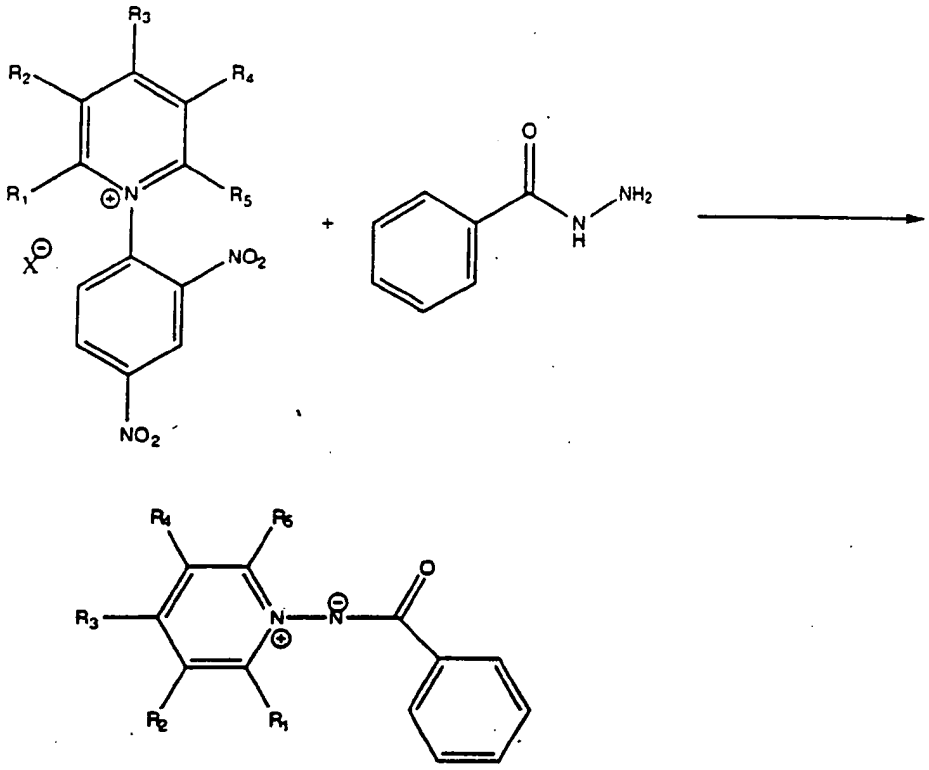
so as to produce polymers of the following structure (shown for the case of reaction with 1,1-dimethylhydrazine):



where X and Y are alkyl, carbocyclic, aryl, aralkyl or alkaryl linkers.

These polymers, which are produced by reacting stoichiometric amounts of the reactants neat or dissolved in lower alcohols or alcohol/water mixtures at temperatures from 20 C to 80 C have been utilized for the case where R = R' as intermediate thermally activated (>150 C) isocyanate precursors for use as crosslinking materials (cf. U.S. patents 3,565,868 and 3,671,473), herein specifically incorporated by reference.

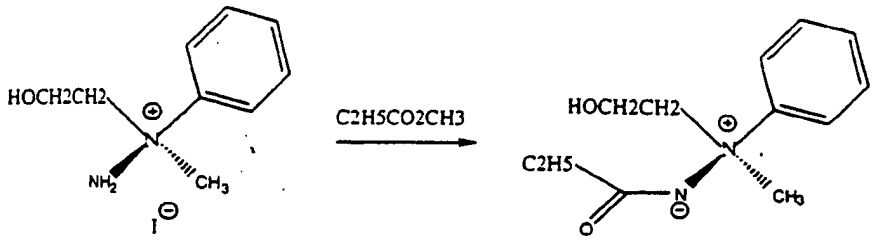
Another aminimide synthesis is the reaction of 2,4-dinitrophenyl pyridinium salts ("Zinke salts") with monosubstituted hydrazones, as shown below (US pat. 4,563,467):



This reaction is carried out by heating equimolar amounts of the pyridinium salt and the hydrazine with a slight excess of triethylamine in an alcohol, such as ethanol, for 12 hours. The desired product is obtained from the precipitated solid produced by extraction with dioxane/water, removal of the dioxane in vacuo, followed by acidification with HCl, filtration to remove salts and neutralizetion with NaOH. The mixture is cooled, the crystallized product is collected by filtration and purified by recrystallization from ethanol (yields 65-85%). Although this reaction suffers from the disadvantage of requiring the removal of the dinitro analine by-product by extraction, it is very useful in forming pyridinium aminimide containing molecules, conjugates, monomers and scaffolds.

4.2.4 Synthesis of Enantiomerically-Pure Aminimides

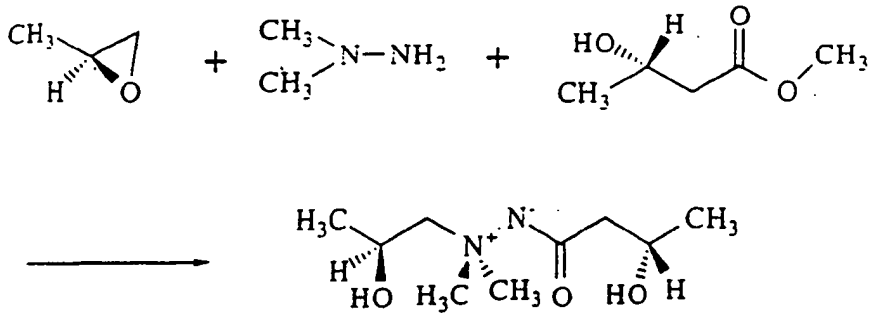
Enantiomerically-pure aminimides may be produced by acylation of chiral hydrazinium salts as shown in the example below.



Chirally-pure hydrazinium salts may be obtained by resolution of the racemates; resolution can be effected by forming salts with optically pure acids, e.g. tartaric acid, and separating the resulting diastereomers by means of chromatography or fractional crystallization (see, e.g., 103 J. Chem. Soc. 604 (1913)); alternatively the racemic modification is resolved by subjecting it to chromatographic separation using a chiral stationary chromatographic support, or if feasible, by the use of a suitable enzyme system.

Enantiomerically-pure aminimides may also be obtained by resolution of the racemic modifications using one of the techniques described above for the resolution of racemic hydrazinium salts (for an example, see 28 J. Org. Chem. 2376 (1963)).

An additional approach to the synthesis of chiral aminimides involves chiral synthesis; an example is provided by the reaction of (S)-(-)-propylene oxide with 1,1-dimethylhydrazine and methyl-(R)-3-hydroxy-butyrate, all of which are commercially available.



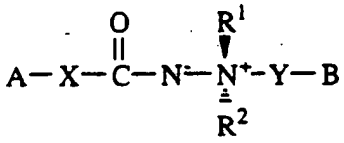
A variety of chiral epoxides, produced by chiral epoxidations such as those developed by Sharpless (Asymm. Syn., J.D. Morrison ed., Vol. 5, Ch. 7 + 8, Acad. Press, New York. N.Y., 1985), and chiral esters, produced by standard procedures, may be used to produce a wide variety of chiral aminimides.

Chirally-pure aminimide molecular building blocks are especially preferred since they can be used to produce a vast array of molecules useful as new materials for high technological applications and as molecular recognition agents. including biological ligand mimetics which can be used as drugs, diagnostics, and separation agents.

4.4 Synthesis of Specific Classes of Aminimides

4.4.1 Synthesis of Chiral Aminimide-Containing Conjugates

The synthetic routes outlined above may be utilized to produce a wide variety of chiral aminimide conjugates of the following general structure:



The substituents A and B may be the same or different and may be of a variety of structures and may differ markedly in their physical or functional properties, or may be the same; they may also be chiral or symmetric. A and B are preferably selected from:

1) amino acid derivatives of the form (AA)N, which would include, for example, natural and synthetic amino acid residues (N=1) including all of the naturally occuring alpha amino acids, especially alanine, arginine, asparagnine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine; the naturally occuring disubstituted amino acids, such as amino isobutyric acid, and isovaline, etc.; a variety of synthetic amino acid residues, including alpha-disubstituted variants, species with olefinic substitution at the alpha position, species having derivatives, variants or mimetics of the naturally occuring side chains; N-Substituted glycine residues; natural and synthetic species known to functionally mimic amino acid residues, such as statine, bestatin, etc. Peptides (N=2-30) constructed from the amino acids listed above, such as angiotensinogen and its family of physiologically important angiotensin hydrolysis products, as well as derivatives, variants and mimetics made from various combinations and permutations of all the natural and synthetic residues listed above. Polypeptides (N=31-70), such as big endothelin, pancreastatin, human growth hormone releasing factor and human pancreatic polypeptide.

Proteins (N>70) including structural proteins such as collagen, functional proteins such as hemoglobin, regulatory proteins such as the dopamine and thrombin receptors.

2) a nucleotide derivative of the form (NUCL)N, which includes natural and synthetic nucleotides (N=1) such as adenosine, thymine, guanidine, uridine, cystosine, derivatives of these and a variety of variants and mimetics of the purine ring, the sugar ring, the phosphate linkage and combinations of

some or all of these. Nucleotide probes (N=2-25) and oligonucleotides (N>25) including all of the various possible homo and heterosynthetic combinations and permutations of the naturally occuring nucleotides, derivatives and variants containing synthetic purine or pyrimidine species or mimics of these, various sugar ring mimetics, and a wide variety of alternate backbone analogues including but not limited to phosphodiester, phosphorothionate, phosphorodithionate, phosphoramidate, alkyl phosphotriester, sulfamate, 3'-thioformacetal, methylene(methylimino), 3-N-carbamate, morpholino carbamate and peptide nucleic acid analogues.

3) a carbohydrate derivative of the form (CH)n. This would include natural physiologically active carbohydrates such as including related compounds such as glucose, galactose, sialic acids, beta-D-glucosylamine and nojorimycin which are both inhibitors of glucosidase, pseudo sugars, such as 5a-carba-2-D-galactopyranose, which is known to inhibit the growth of Klebsiella pneumonia (n=1), synthetic carbohydrate residues and derivatives of these (n=1) and all of the complex oligomeric permutations of these as found in nature, including high mannose oligosaccharides, the known antibiotic streptomycin (n>1).

4) a naturally occurring or synthetic organic structural motif. This term is defined as meaning an organic molecule having a specific structure that has biological activity, such as having a complementary structure to an enzyme, for instance. This term includes any of the well known base structures of pharmaceutical compounds including pharmacophores or metabolites thereof. These include beta-lactams, such as pennicillin, known to inhibit bacterial cell wall biosynthesis; dibenzazepines, known to bind to CNS receptors, used as antidepressants; polyketide macrolides, known to bind to bacterial ribosymes, etc. These structural motifs are generally known to have specific desirable binding properties to ligand acceptors.

5) a reporter element such as a natural or synthetic dye or a residue capable of photographic amplification which possesses reactive groups which may be synthetically incorporated into the aminimide structure or reaction scheme and may be attached through the groups without adversely interfering with the reporting functionality of the group. Preferred reactive groups are amino, thio, hydroxy, carboxylic acid, carboxylic acid ester, particularly methyl ester, acid chloride, isocyanate alkyl halides, aryl halides and oxirane' groups.

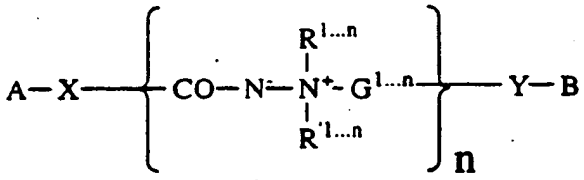
6) an organic moiety containing a polymerizable group such as a double bond or other functionalities capable of undergoing condensation polymerization or copolymerization. Suitable groups include vinyl groups, oxirane groups, carboxylic acids, acid chlorides, esters, amides, lactones and lactams. Other organic moiety such as those defined for R and R' may also be used.

7) a macromolecular component, such as a macromolecular surface or structures which may be attached to the aminimide modules via the various reactive groups outlined above in a manner where the binding of the attached species to a ligand-receptor molecule is not adversely affected and the interactive activity of the attached functionality is determined or limited by the macromolecule. This includes porous and non-porous inorganic macromolecular components, such as, for example, silica, alumina, zirconia, titania and the like, as commonly used for various applications, such as normal and reverse phase chromatographic separations, water purification, pigments for paints, etc.; porous and non-porous organic macromolecular components, including synthetic components such as styrene-divinyl benzene beads, various methacrylate beads, PVA beads, and the like, commonly used for protein purification, water softening and a variety of other applications, natural components such as native and functionalized celluloses, such as, for example, agarose and chitin, sheet and hollow fiber membranes made from nylon,

polyether sulfone or any of the materials mentioned above. The molecular weight of these macromolecules may range from about 1000 Daltons to as high as possible. They may take the form of nanoparticles (dp=100-1000Angstroms), latex particles (dp=1000-5000Angstroms), porous or non-porous beads (dp=0.5-1000 microns), membranes, gels, macroscopic surfaces or functionalized or coated versions or composites of these.

A and/or B may be a chemical bond to a suitable organic moiety, a hydrogen atom, an organic moiety which contains a suitable electrophilic group, such as an aldehyde, ester, alkyl halide, ketone, nitrile, epoxide or the like, a suitable nucleophilic group, such as a hydroxyl, amino, carboxylate, amide, carbanion, urea or the like, or one of the R groups defined below. In addition, A and B may join to form a ring or structure which connects to the ends of the repeating unit of the compound defined by the preceding formula or may be separately connected to other moieties.

A more generalized structure of the composition of this invention is defined by the following formula:



wherein:

a. at least one of A and B are as defined above and A and B are optionally connected to each other or to other compounds;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each represents B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

As used herein, the phrase linear chain or branched chained alkyl groups means any substituted or unsubstituted acyclic carbon-containing compounds, including alkanes, alkenes and alkynes. Alkyl groups having up to 30 carbon atoms are preferred. Examples of alkyl groups include lower alkyl, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl; upper alkyl, for example, cotyl, nonyl, decyl, and the like; lower alkylene, for example, ethylene, propylene, propyldiene, butylene, butyldiene; upper alkenyl such as 1-decene, 1-nonene, 2,6-dimethyl-5-octenyl, 6-ethyl-5-octenyl or heptenyl, and the like; alkynyl such as 1-ethynyl, 2-butynyl, 1-pentynyl and the like. The ordinary skilled artisan is familiar with numerous linear and branched alkyl groups, which are within the scope of the present invention.

In addition, such alkyl group may also contain various substituents in which one or more hydrogen atoms has been replaced by a functional group. Functional groups include but are not limited to hydroxyl, amino, carboxyl, amide, ester, ether, and halogen (fluorine, chlorine, bromine and iodine), to mention but a few. Specific substituted alkyl groups can be, for example, alkoxy such as methoxy, ethoxy, butoxy, pentoxy and the like, polyhydroxy such as 1,2-dihydroxypropyl, 1,4-dihydroxy-1-butyl , and the like; methylamino, ethylamino, dimethylamino, diethylamino, triethylamino, cyclopentylamino, benzylamino, dibenzylamino, and the like; propanoic, butanoic or pentanoic acid groups, and the like; formamido, acetamido, butanamido, and the like, methoxycarbonyl, ethoxycarbonyl or the like, chloroformyl, bromoformyl, 1,1-chloroethyl, bromo

ethyl ,and the like. or dimethyl or diethyl ether groups or the like.

As used herein, substituted and unsubstituted carbocyclic groups of up to about 20 carbon atoms means cyclic carbon-containing compounds, including but not limited to cyclopentyl, cyclohexyl, cycloheptyl, admantyl, and the like. such cyclic groups may also contain various substituents in which one or more hydrogen atoms has been replaced by a functional group. Such functional groups include those described above, and lower alkyl groups as described above. The cyclic groups of the invention may further comprise a heteroatom. For example, in a specific embodiment, R_2 is cycohexanol.

As used herein, substituted and unsubstituted aryl groups means a hydrocarbon ring bearing a system of conjugated double bonds, usually comprising an even number of 6 or more (pi) electrons. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, anisyl, toluyl, xylenyl and the like. According to the present invention, aryl also includes aryloxy, aralkyl, aralkyloxy and heteroaryl groups, e.g., pyrimidine, morpholine, piperazine, piperidine, benzoic acid, toluene or thiophene and the like. These aryl groups may also be substituted with any number of a variety of functional groups. In addition to the functional groups described above in connection with substituted alkyl groups and carbocylic groups, functional groups on the aryl groups can be nitro groups.

As mentioned above, R_2 can also represent any combination of alkyl, carbocyclic or aryl groups, for example, 1-cyclohexylpropyl, benzylcyclohexylmethyl, 2-cyclohexyl-propyl, 2,2-methylcyclohexylpropyl, 2,2methylphenylpropyl, 2,2-methylphenylbutyl, and the like.

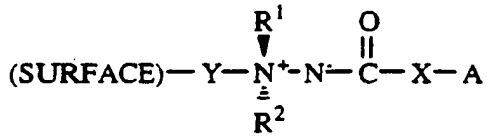
d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

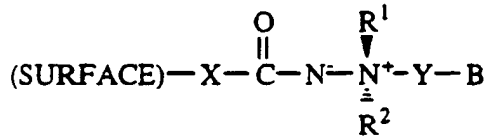
e. n is equal to or greater than 1.

Preferably, if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and if n is 1 and X and Y are chemical bonds, R and R' are the same, A and B are different and one is other than H or R. Also, when A is a substituted benzene ring, the meta position will not be substituted with an SO_2NH_2 group when n =1, X is a C-C bond and R and R' together form a trimethyl substituted pyridine ring.

In one embodiment of the invention, at least one of A and B represents an organic or inorganic macromolecular surface. Examples of preferred macromolecular surfaces include ceramics such as silica and alumina, porous and nonporous beads, polymers such as a latex in the form of beads, membranes, gels, macroscopic surfaces or coated versions or composites or hybrids thereof. This functionalized surface may be represented as follows:

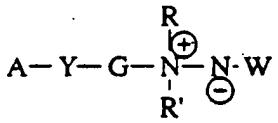


In a further embodiment of the invention, the above roles of A and B are reversed, so that B is the substituent selected from the foregoing list and A represents a functionalized surface, as shown below:



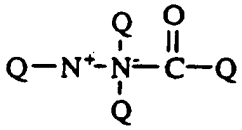
In a third preferred embodiment of the invention, either A, B, or both contain one or more double bonds capable of undergoing free-radical polymerization or copolymerization to produce achiral or chiral oligomers, polymers, copolymers, etc.

Another embodiment of the invention relates to a composition having the structure:



wherein A, Y, R, R1 and G are as defined above and W is -H or -H2X- where X- is an anion, such as a halogen or tosyl anion.

Yet another aspect of the invention relates to a lipid mimetic composition having the structure

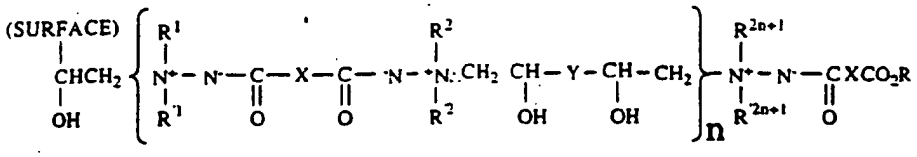


wherein Q is a chemical bond; hydrogen; an electrophilic group; a nucleophilic group; R; an amino acid derivative; a nucleotide derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; a macromolecular component; or the substituent X(T) or X(T)2; wherein R is an alkyl, carbocyclic, aryl, aralkyl or alkaryl group or a substituted or heterocyclic derivative thereof, and T is a linear or branched hydrocarbon having between 12 and 20 carbon atoms some of which are optionally substituted with oxygen, nitrogen or sulfur atoms or

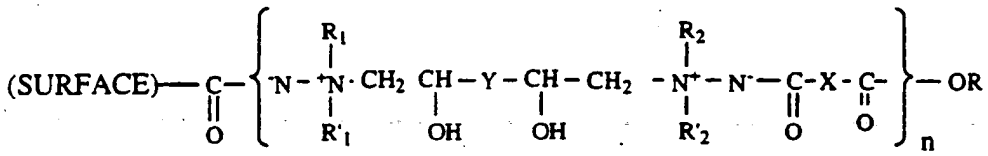
by an aromatic ring; and provided that at least two T substituents are present in the structure of the composition.

In the description that follows, Rn where n is an integer will be used to designate a group from the definition of R and R1.

Another aspect of the invention relates to functionalized polymers having the structure:



or



wherein

a. X and Y are connecting groups;

b. R1n or R'1n (where n = an integer) each represent alkyl, cycloalkyl, aryl, aralkyl and alkaryl;

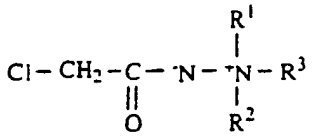
c. (SURFACE) is a macromolecular component; and

d. n is equal to or greater than 1.

These functionalized polymers may be made according to known techniques for attaching terminal groups to the surface or by attaching a monomer unit to the surface and then building the polymer, for instance.

The invention also encompasses various methods of producing an aminimide-functional support. One method comprises the steps of reacting a polymer or oligomer

containing pendant moieties of OH, NH or SH with a compound of the formula:



wherein R1 and R2 each represent alkyl, carbocyclic, aryl, aralkyl or alkaryl, and R3 is an amino acid derivative; a nucleotide derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component; coating the reacted polymer or oligomer onto a support to form a film thereon; and heating the coated support to crosslink the film.

Another method comprises the steps of coating a mixture of multifunctional esters and multifunctional epoxides onto a support to form a film thereon; and reacting the coated support with 1,1'-dialkylhydrazine to crosslink the film.

A third method comprises the steps of coating a mixture of an aminimide-functional vinyl monomer, a difunctional vinyl monomer and a vinyl polymerization initiator onto a support to form a film thereon; and heating the coating support to form a crosslinked film.

The aminimide-functionalized support prepared according to the previous methods are another aspect of the invention.

The ability to derivatize an aminimide scaffold in numerous ways using the synthetic techniques outlined above as well as those given below, offers a vast array of structures capable of recognizing specific molecular entities via establishment of specific types of binding interactions. Thus the aminimide shown below is in principle capable of establishing the following interactions: π-stacking involving

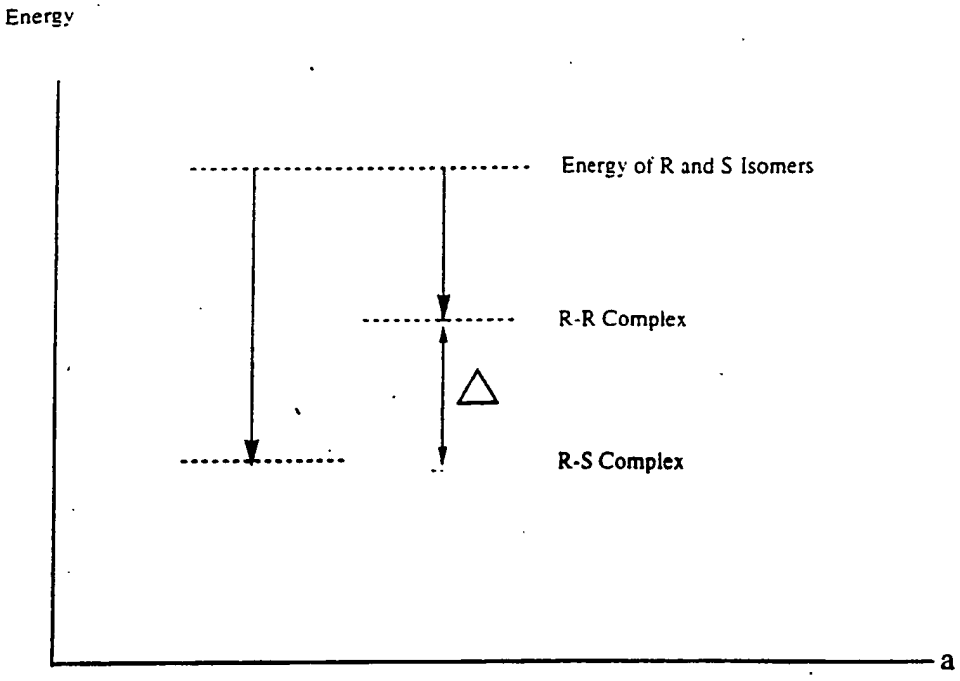
the phenyl group; hydrogen bonds; acid-base interactions involving the anionic nitrogen; salt bridges involving the quaternary nitrogen; steric interactions with the bulky isopropyl substituent; and hydrophobic interactions involving the hydrocarbon chain.

Chiral Recognition

"Chiral recognition" is a process whereby chiral enantiomers display differential binding energies with an enantiomerically pure chiral target or recognition agent. This agent may be attached to a surface to produce a chiral stationary phase (CSP) for chromatographic use or may be used to form diastereomeric complexes with the racemic target. These complexes have differing physiochemical propereties which allow them to be separated using standard unit processes, such as fractional crystallization.

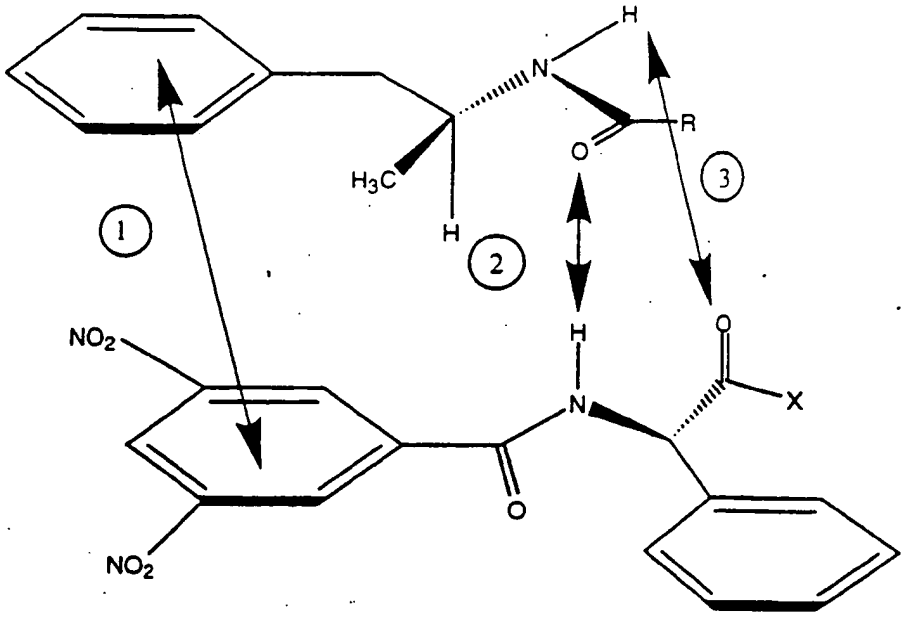
Two steps are necessary for the recognition process to occur with a CSP; 1.) absorption and 2.) energetic differentiation between the enantiomers. The absolute binding energies between the enantiomers and the surface determine the tightness of the binding. The difference in energy between the complexes determines the selectivity. This is represented in the following diagram

The interaction of the enantiomeric R and S species with the CSP can be envisioned as a "three point interaction". This does not mean that three actual points of attachment or

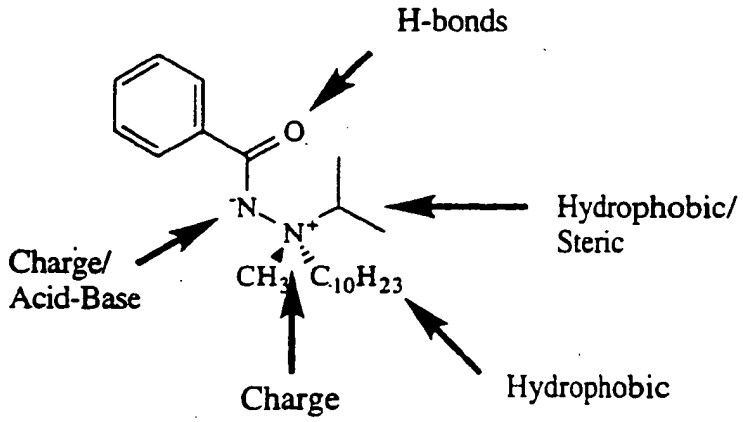


association are necessary, but rather that any three kinds of attractive or repulsive interactions within the diastereomeric complexes can serve to differentiate ("recognize") the enantiomers. Greater differentiation ("recognition") betwen the complexes is promoted by multiple combinations of attractive and/or repulsive interactions, including hydrogen bonding, ionic interactions, dipole interactions, hydrophobic, pi-pi interactions and steric interactions between the two chiral species. The larger the number and the more varied the types of these interactions, the greater the resulting energy differences between the complexex and the greater the degree of "recognition" per interaction.

"Three point interaction"

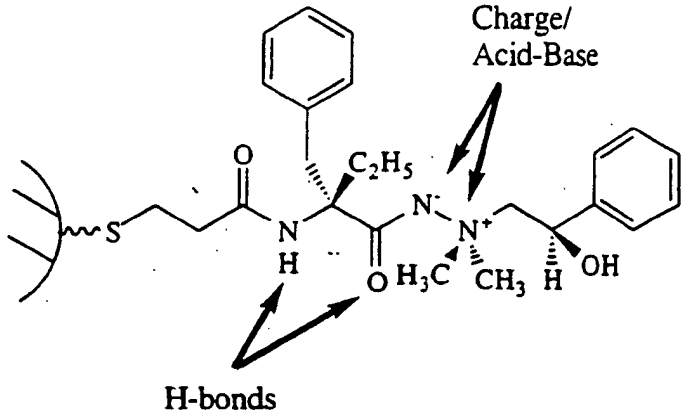


The possible modes of interaction which can participate in such "three point inyteractions" is depicted below for a enantiomerically pure aminimide.



As a further example, possible interactions between a recognition target and a specific supported aminimide are

shown below. Experimental procedures for the synthesis of specific chiral aminimides are given below.



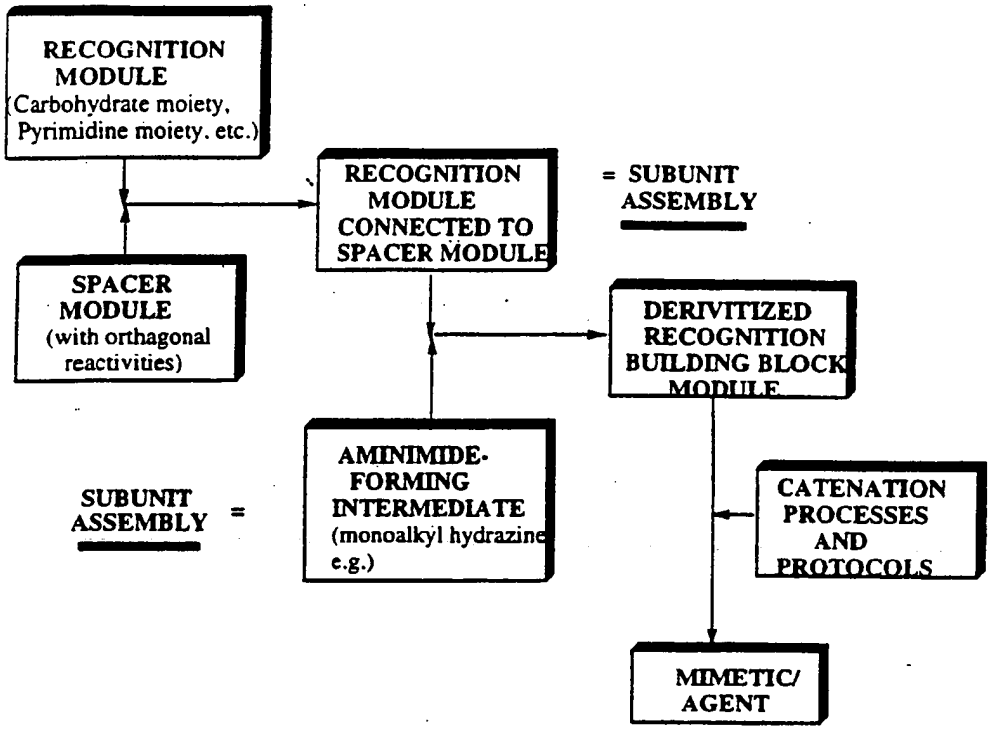
4.4.2 Sequential Catenation of Aminimide Subunits Producing Sequences of Various Sizes

By choosing aminimide building blocks possessing functional groups capable of establishing predictable binding interactions with target molecules, and by using synthetic techniques such as those broadly described above to effect catenation (linking) of the building blocks, it is possible to construct sequences of aminimide subunits mimicking selected native oligomers or polymers, e.g., peptides and polypeptides. oligonucleotides, carbohydrates, as well as any other biologically active species whose three dimensional binding geometry can be mimicked by various combinations of aminimide-containing scaffolds and side chains. This may be accomplished using a wide variety of side chain recognition group substituents including, but not limited to, the substituents found in the side chains of naturally occuring amino acids; purine and pyrimidine groups, as well as derivatives and variants of these; natural and synthetic carbohydrate recognition groups, such as sialic acids; groups containing organic structures with known pharmacological activities, such as beta lactam antibiotic moities, which are known to be efficient inhibitors of bacterial cell wall biosynthesis, to produce structures which have highly specific activities. These moieties may be attached, arranged and spaced in a position-specific manner along a scaffold whose basic geometry, spacing, rigidity and other properties can be designed and locally tuned to functionally mimic the natural scaffolds found in peptides, proteins, oligonucleotides or carbohydrates; or which can simply serve to array sequences or combinations of these side chain recognition groups in an appropriate structural relationships to the scaffold and to each other to produce species with highly specific and selective activity. In addition, because of the inherent hydrolytic and enzymatic stability and solubilizing properties of the

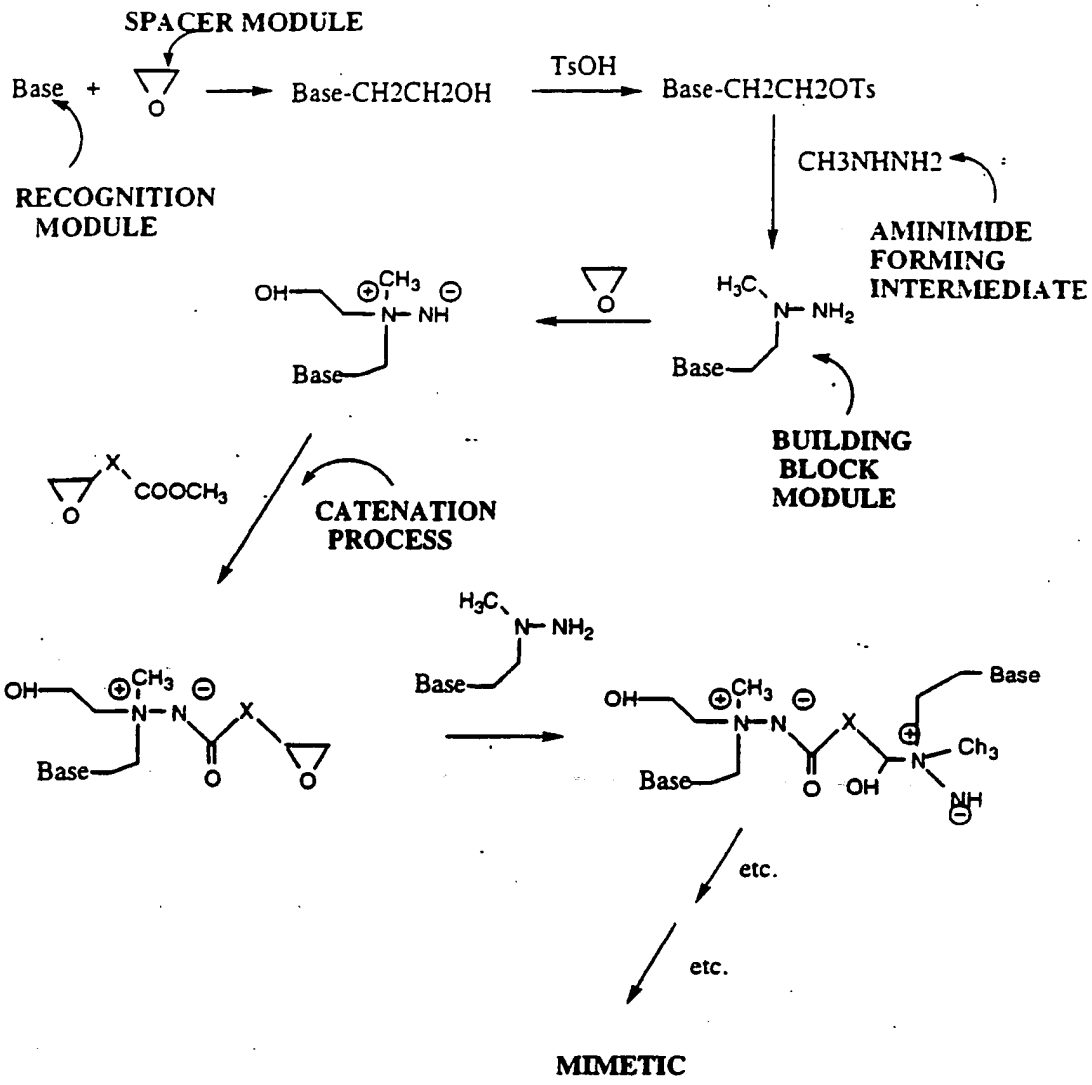
properties of the aminimide linkage, these designed functional molecules will have better stability and pharmacokinetic properties than those of the native species. The integrated modularity of the chemistries allows the construction of this wide variety of molecules to be carried out in a manner analogous to the design of an electronic device by combining component subsystems using a relatively small number of interchangable reactive modules and protocols. This is figuratively outlined below.

It should be apparent to those skilled in the art that other compositions and processes for preparing the compositions not specifically disclosed in the instant specification are, nevertheless, contemplated thereby. such other compositions and processes are considered to be within the scope and spirit of the present invention. Hence, the invention should not be limited by the description of the specific embodiments disclosed herein but only by the folowing claims.

MODULAR DESIGN AND ASSEMBLY FLOW CHART



The generic concept is illustrated below for the introduction of a generic "base" (purine or pyrimidine) into an aminimide scaffold as a hydrazine equivalent connected via a spacer. While the example uses a base as the recognition group, it should be kept in mind that this group could equally well be a carbohydrate, a pharmacophore moiety or a designed synthetic recognition element.



Specific syntheses of multisubunit aminimides are outlined below:

4.4.2.1 Catenation of Aminimide Subunits via Acylation/Alkylation Cycles

The following steps are involved in this synthesis:

1. Acylation of a chiral hydrazinium salt, prepared as described above, with a molecule capable of functioning both as an acylating and as an alkylating agent producing an aminimide; BrCH2COCl and other bifunctional species, such as bromoalkyl isocyanates, 2-bromoalkyl oxazolones, etc., may be used as acylating agents under the reaction conditions given above.

2. Further reaction of the product from the above reaction with an asymmetrically disubstituted hydrazine to form a diastereomeric mixture of aminimide hydrazinium salts under reaction conditions similar to those described above.

3. Isolation of the diastereomers produced in Step 2 as described above, e.g., by fractional crystallization or by chromatography using techniques familiar to those skilled in the art.

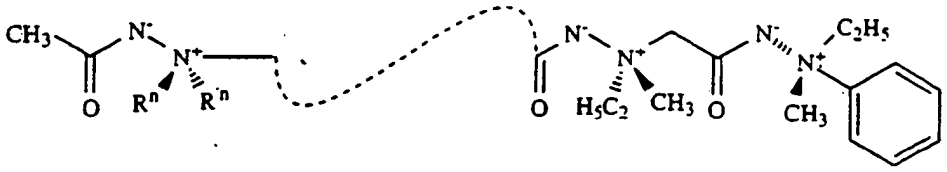
4. Acylation of the desired diastereomer from Step 3 with a bifunctional acyl derivative similar to those listed in Step 1 above producing a dimeric type structure.

5. Repetition of Steps 2, 3 and 4 the required number of times to build the desired aminimide subunit sequence.

6. Capping of the assembled sequence, if desired, for example, by reaction with an acylating agent, such as acetyl chloride.

The experimental conditions (e.g. reaction-solvent, temperature and time, and purification procedures for products) for all of the above reactions were described above and are also well-known and practiced in the art. As the molecular weight of the products increases (e.g. in step 5 above) solubility and reaction-rate problems may develop if the reactions are run under the conditions that successfully gave products of smaller molecular weight. As is well known from the art of peptide synthesis, these problems are probably due to conformational (folding) effects and to aggregation

phenomena, and procedures found to work in the related peptide cases are expected to be very useful in the case of aminimide catenations. For example, reaction solvents such as DMF, or N-methyl pyrollidone, and chaotropic (aggregate-breaking) agents, such as urea, are expected to be helpful in alleviating reactivity problems as the molecular-weight of the product increases.



4.4.2.2 Catenation of Aminimide Subunits via Alkylation/Acylation Cycles

The following steps are involved in this synthesis; experimental conditions for running the reactions are similar to those given for the corresponding steps in the above catenation scheme.

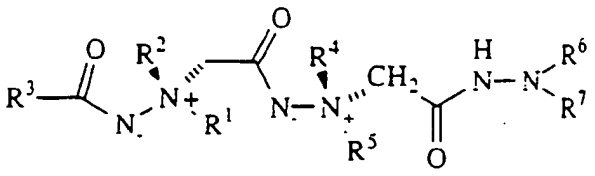
1. Alkylation of an asymmetrically disubstituted hydrazide, prepared as outlined above, with a molecule capable of functioning both as an alkylating and an acylating agent to form a racemic mixture of aminimides; as before the use of BrCH2COCl is shown below, but other bifunctional species, such as bromoalkyl isocyanates, 2-bromoalkyl oxazolones, etc. may also be used.

2. Reaction of the racemate from above with an asymmetrically disubstituted hydrazine to form the hydrazide.

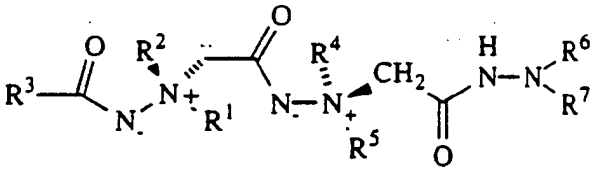
3. Resolution of the racemic modification from the previous step as described above.

4. Alkylation of the product from step 3 with a bifunctional molecule capable of alkylation and acylation, which may be the same as that used in step 1 or different, to form a mixture of diastereomeric aminimides.

5. Reaction of the diastereomers from step 4 with a suitable asymmetrically disubstituted hydrazine to form the diastereomeric hydrazides, as shown:



+



6. Separation of the diastereomers as described above.

7. Repetition of steps 4, 5 and 6 to build the desired sequence of aminimide subunits.

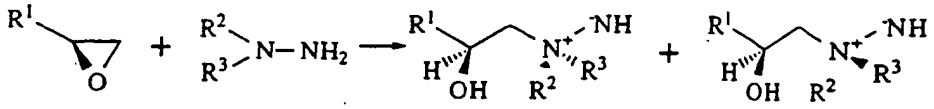
8. Capping of the sequence, if desired, using e.g. methyl bromide to produce a sequence such as shown below.

4.4.2.3 Catenation of Aminimide Subunits Using Hydrazinolysis of an Ester in the Presence of an Epoxide

The following steps are involved in this synthesis; experimental conditions for running the reactions are given above.

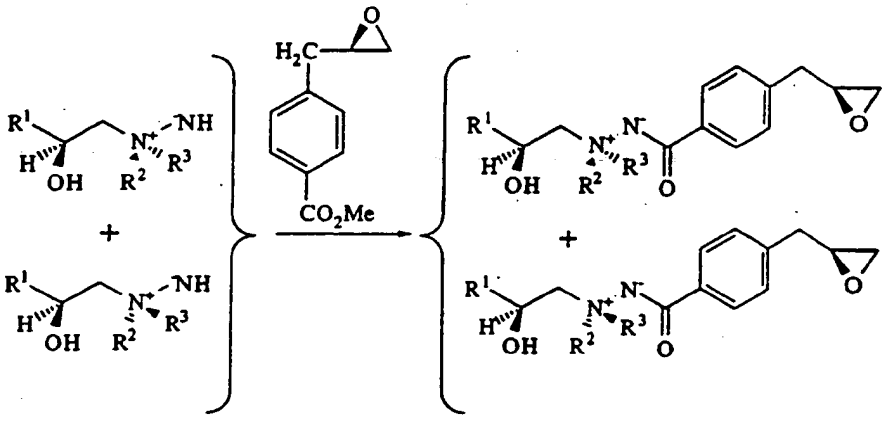
1. Formation of an aminimine from the reaction of an 1,1-asymmetrically disubstituted hydrazine with an

epoxide; the reaction is illustrated for a chiral epoxide below (the chiral epoxide may be obtained by e.g. a Sharpless epoxidation):



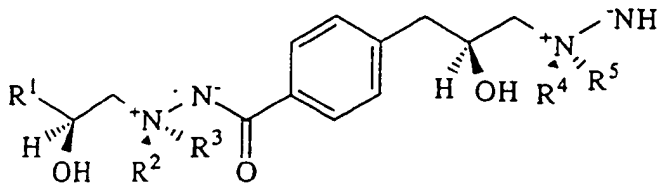
The aminimine is normally not isolated, but used directly for the following reaction.

2. The aminimine is reacted with an ester-epoxide to give an aminimine; for the mixture of diastereomeric aminimides above and the ester-epoxide shown below, the following is obtained.



3. Separation of the diastereomeric aminimides as described above.

4. Reaction of the desired diastereomeric aminimide with an asymmetrically disubstituted hydrazine to form diastereomeric aminimide-aminimines:



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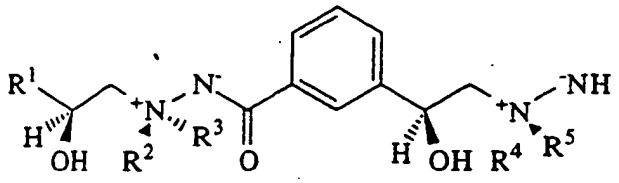
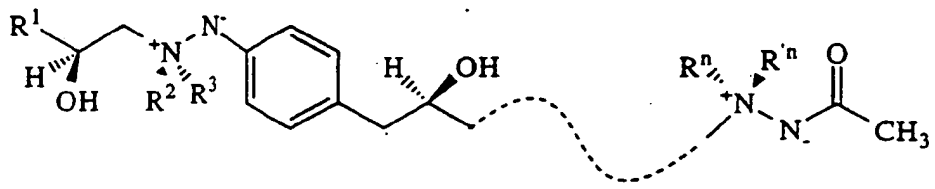


5. Repetition of steps 2, 3 and 4 above using the appropriate hydrazines and epoxy-esters in each step to produce the desired aminimide sequence.

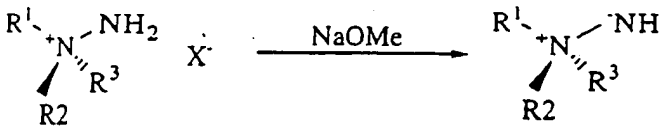
6. "Capping" of the final sequence, if desired, by acylation with a simple ester, such as methyl acetate, to produce the designed aminimide ligand shown:



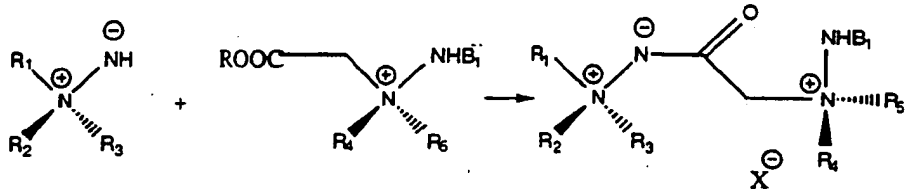
4.4.2.4 Catenation of alpha-Hydrazinium Esters or Carboxylic Acids

The following steps are involved in this synthesis; experimental conditions for running the reaction are given above.

1. Treatment of a chirally-pure hydrazinium salt (produced as described above) with a strong base, such as NaOMe in an alcohol solvent, to form the imino anion:

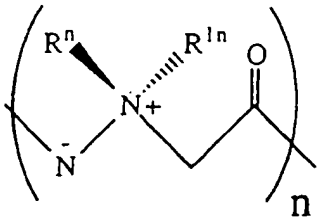


2. Addition of an Alpha-Hydrazinium ester (again produced as discussed above) to an appropriately blocked imino-anion-containing mixture from step 1 to form the hydrazinium-aminimide, as shown.



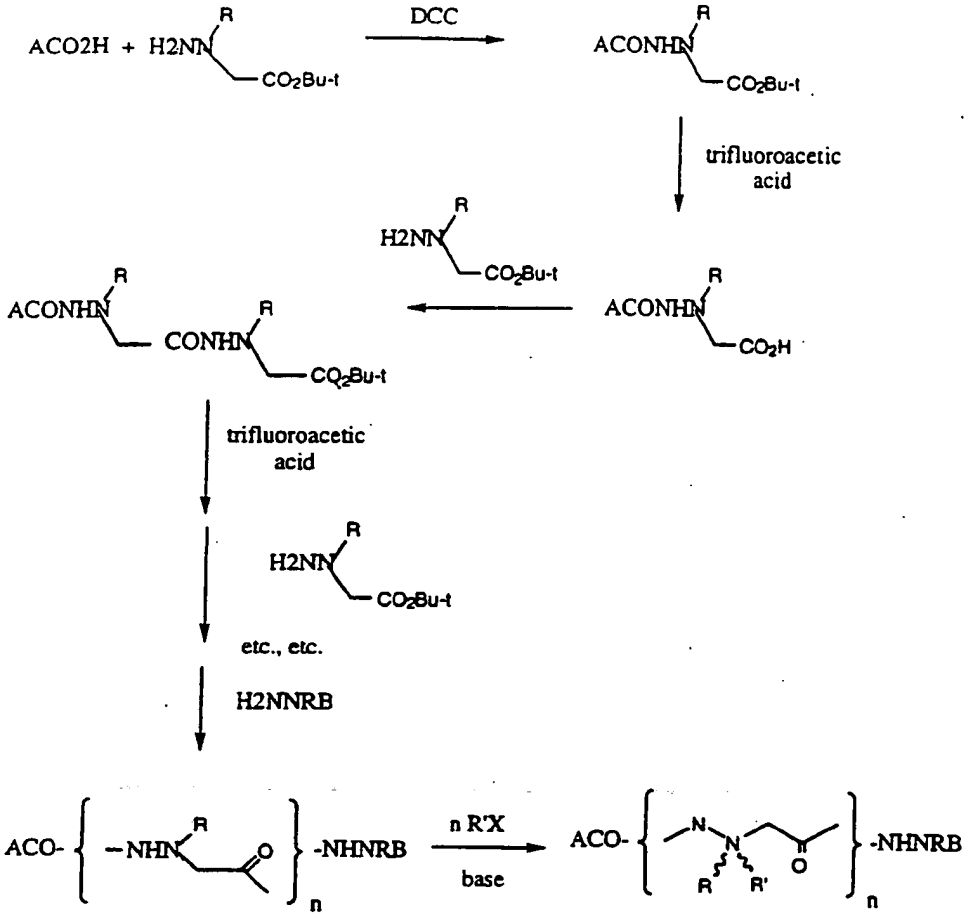
In the equation above, B1 is an appropriate protecting group such as BOC (*t*-butyl carbamate), particularly suitable for this purpose, readily cleaved by acid hydrolysis; 2,4-dichlorobenzene carbamate, cleaved by acid hydrolysis, but more stable than BOC; 2-(biphenylyl)isopropyl carbamate, cleaved more easily than BOC by dilute acid; FMOC (9-fluorenylmethyl carbamate), cleaved by ß-elimination with base; isonicotinyl carbamate, cleaved by reduction with zinc in acetic acid; 1-adamantyl carbamate, readily cleaved by trifluoroacetic acid; 2-phenylisopropyl carbamate, cleaved by acid hydrolysis but slightly more stable than BOC; imines and enamines, readily cleaved by acid hydrolysis; mono and bis trialkylsilyl derivatives, cleaved by heating in water or in the presence of fluoride ion; phosphinamides and some sulfenamides, which are cleaved by mild acid hydrolysis; and alkylsulfonamides, cleaved by strong acid hydrolysis.

3. Removal of B1 followed by repetition of steps 1 and 2 the required number of times to obtain the desired aminimide sequence, followed by a "capping" step, using a simple ester as acylating agent.



Alternatively, the alpha-hydrazinium carboxylic acids may be obtained by treatment of the esters with LiOH in MeOH/H2O at room temperature, as described above, and coupled with each other using condensation reactions promoted by DCC or other agents. Protecting groups used in traditional peptide synthesis are expected to be useful here as well.

An alternate strategy is to catenate sequences of substituted hydrazides to obtain ligands with the desired side-chain substitution patterns, and subsequently convert all of the hydrazide groups to aminimides by multiple simultaneous alkylation followed by neutralization. This approach, which is outlined below, does not allow stereochemical control of the chiral center and, as a result, each aminimide center formed will exist as a racemic mixture. However, the hydrazide oligomers themselves may, in fact, serve as useful binding ligands.



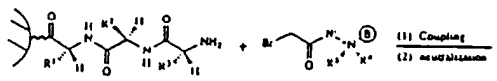
Representative examples of assemblage of a hydrazinium-based scaffold via iterative hydrazide homologation and subsequent alkylation are set forth in examples below.

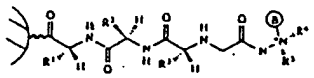
4.4.3 Synthesis of Aminimide-Containing Peptides and Proteins

Aminimide subunits may be introduced into any position of a polypeptide via chemical synthesis, using one of the procedures outlined above, including the techniques for dealing with problematic reactions of high molecular weight species. The resulting hybrid molecules have improved properties over the native molecules; for example, the

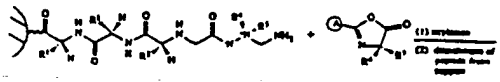
aminimide group can confer greater hydrolytic and enzymatic stability to the hybrid molecule over its native counterpart.

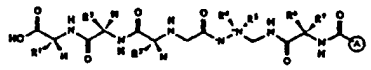
As an example of a synthesis of an aminimide-modified peptide, the modification of a peptide attached to a Merrifield solid phase synthesis support by alkylation with aminimide-containing molecule is shown below.





If moiety B contains a functional group which can be used to link additional aminimide and natural or unnatural amino acid subunits, e.g. via acylation reactions, complex hybrid structures may be obtained using the experimental procedures outlined above.





4.4.4 Synthesis of Oligonucleotide Mimetics

As discussed previously, much attention has been focused on the construction and application of molecules which possess the property of binding to nucleic acids. In the course of work in this area, a great amount of knowledge has been amassed vis-a-vis 1.) the ability of a synthetic scaffold to support a series of natural or designed bases in such a manner that tight binding to natural nucleic acids is observed; 2.) the requirements for designed or naturally occuring bases other than guanocine, cytosine, thymidine, adenosine or uridine to efficiently bind (hybridize) to another natural base or nucleotide. It has been demonstrated that even unnatural or modified bases can show efficient hybridization if projected from an effective scaffold. Our strategy, disclosed herein, is to append natural and/or unnatural bases (e.g. thymine, guanidine, 5-fluorouricil(5FU)) onto aminimide backbones to

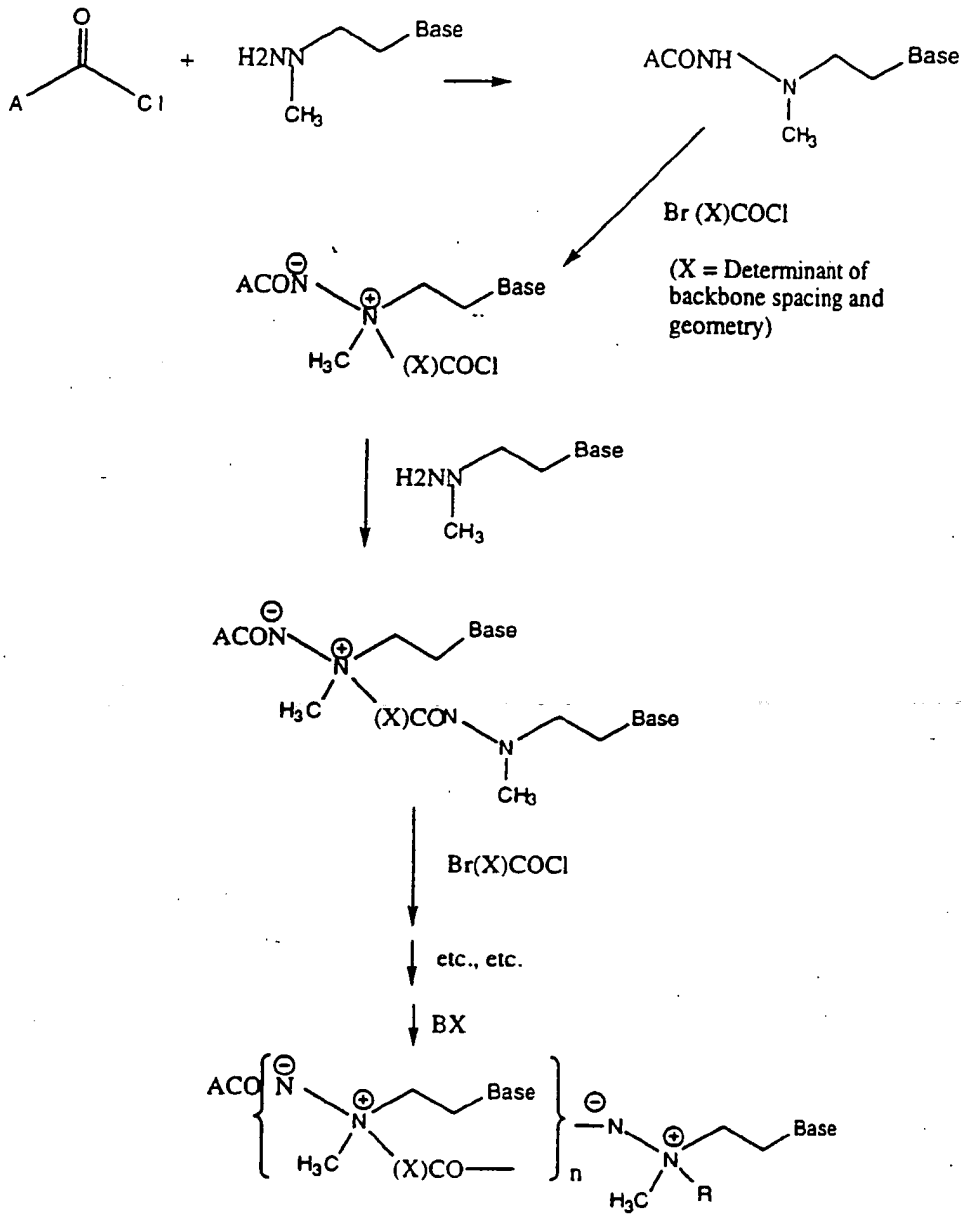
form an antisense strand, or nucleotide mimetic. The resulting linkages and backbones are superior in their resistance to base, acid and proteolytic/phospholytic activity. The bases can be attached using appropriate spacers and the stereochemistry and periodiocity of substitution geometry and rigidity of the backbone scaffold can be designed such that the bases are geometrically arrayed and projected to provide the optimum arrangement and orientation of the bases to hybridize with their targeted counterparts.

Aminimide oligonucleotide mimetics can be produced using the aminimide forming and catenation chemistries outlined above so as to produce aminimide backbones having natural or synthetic bases attached as side chain substituents to the backbone via appropriate spacers, i.e. R or R' in the general structural formulas described above designates the Base-spacer grouping.

This may be accomplished via the following general synthesis schemes:

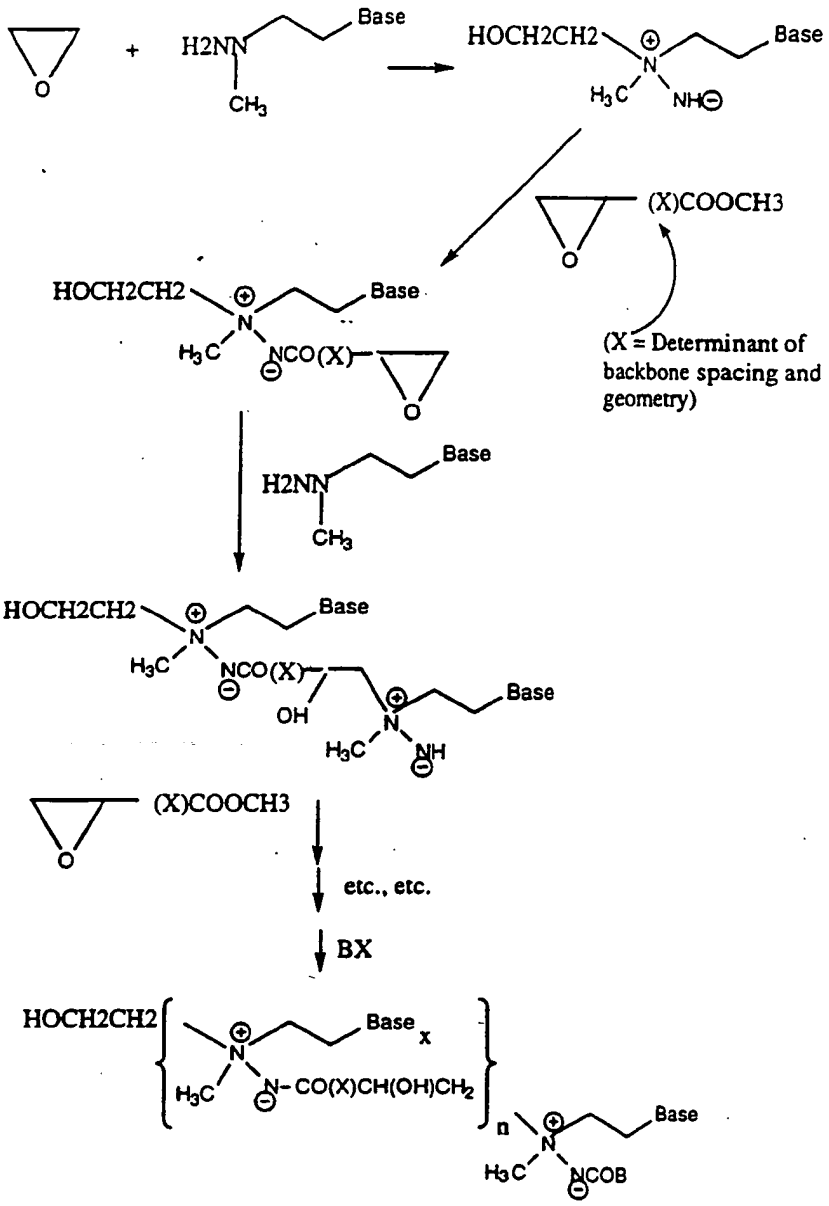
I. Sequential Acylation/Alkylation Reactions Using Base-Functionalized Hydrazines - This is outlined for the Acylation/alkylation case below:

I. Sequential Acylation/Alkylation Reactions Using Base-Functionalized Hydrazines

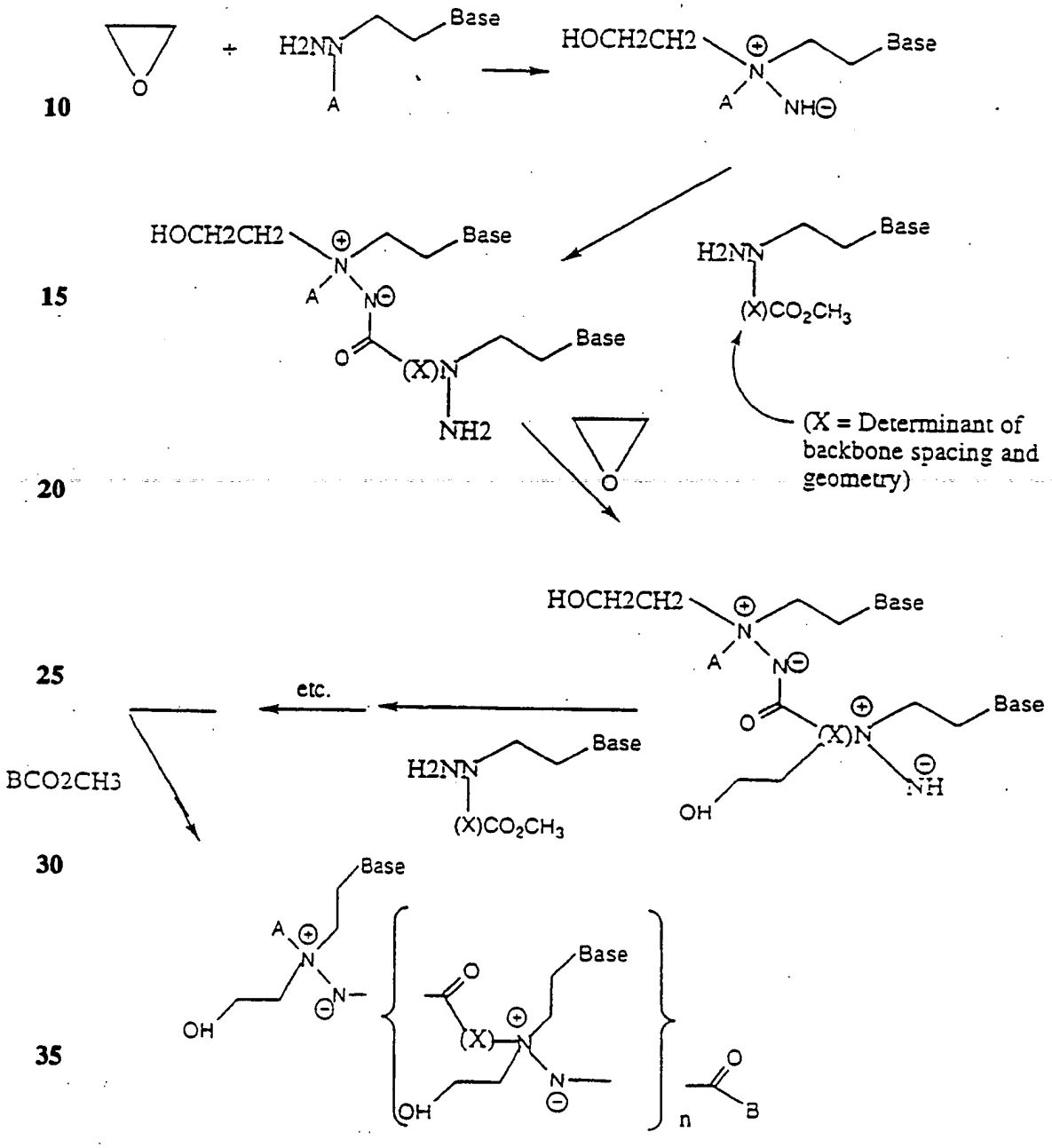


II. Sequential Epoxide/Ester/Hydrazine Reactions

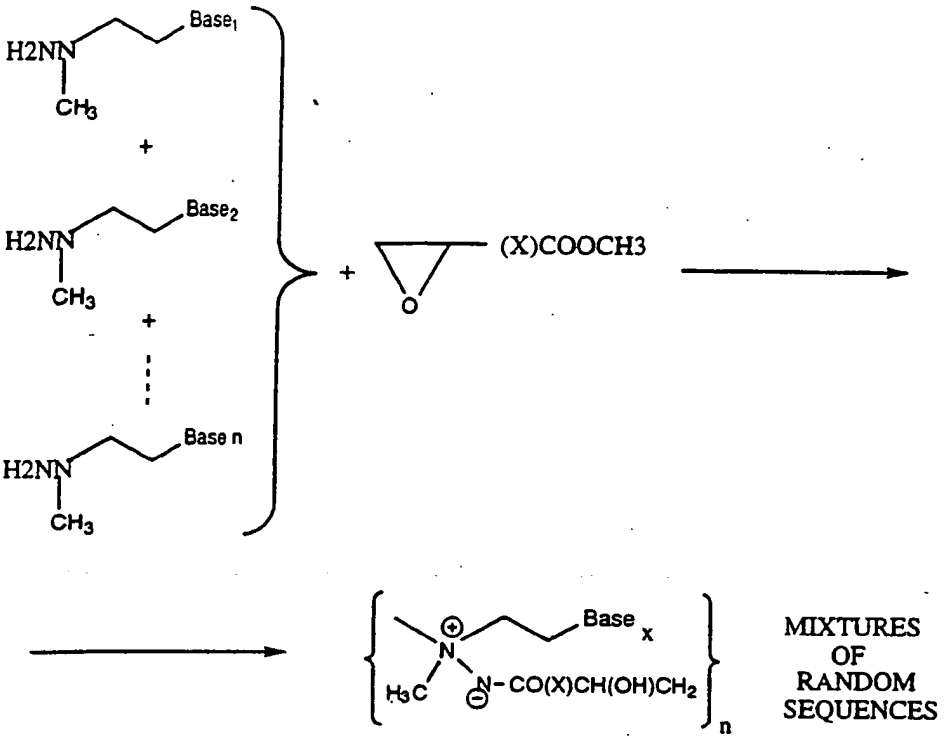
a. Bifunctional Epoxide-Esters With Base-Functionalized Hydrazines



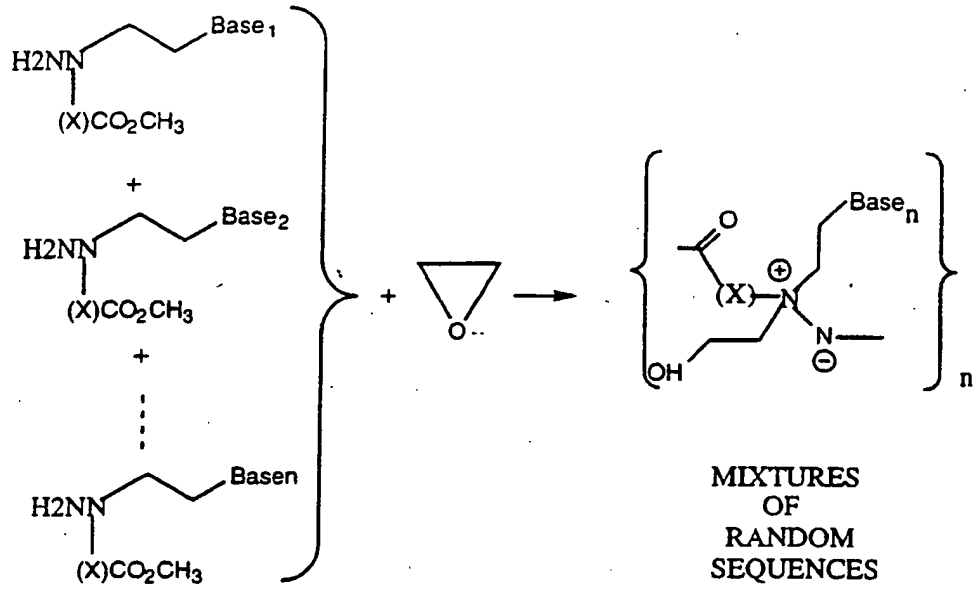
E 5. BASE-FUNCTIONALIZED CARBOXYESTER-HYDRAZINE



Alternatively, these reactions may be carried out in a concerted manner with mixtures of base-functionalized hydrazines to produce random oligonucleotide sequences which can be screened for activity, as outlined: a.)



b.)



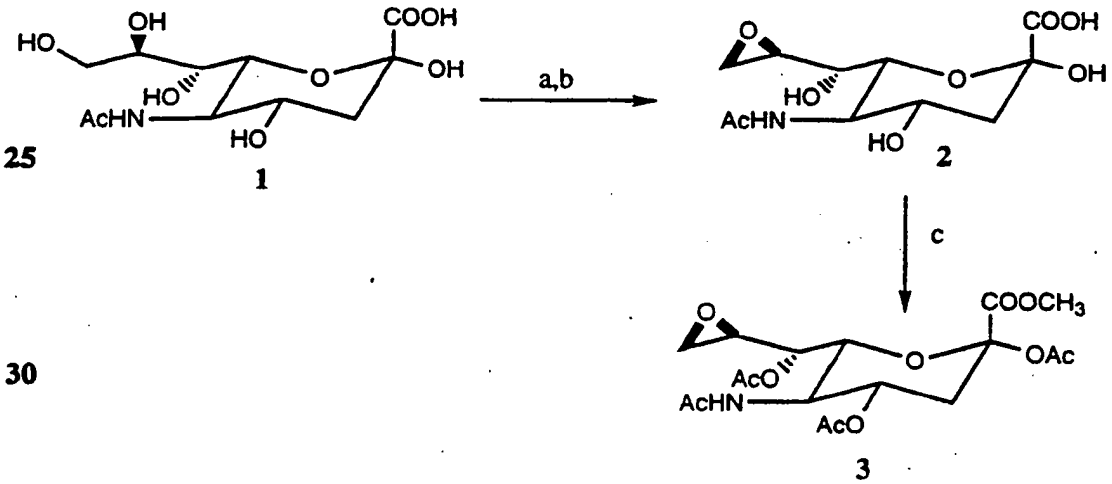
4.4.5 Synthesis of Carbohydrate Mimetics

As mentioned previously, carbohydrates increasingly are being viewed as the components of living systems with the enormously complex structures required for the encoding of the massive amounts of information needed to orchestrate the processes of life, e.g., cellular recognition, immunity, embryonic development, carcinogenesis and cell-death. This information is contained and utilized through highly specific binding interactions mediated by the detailed three dimensional-topological form of the specific carbohydrate. It is of great value to be able to arrange and to connect these moities in various arrays in a controlled manner. This may be done either by connecting carbohydrate recognition groups along an oligomeric backbone, as done by for random vinyl copolymers containing functionalized sialic acid groups, which were shown to inhibit hemagluttinin binding (J. Am. Chem. Soc., 113, 686, 1991) or by arranging multiple carbohydrate groups with appropriate spacers on a suitable structural scaffold so

carbohydrate groups are oriented in space in such a way that they can bind selectively to the target (cf., eg., J. Am. Chem. Soc., 113, 5865, 1991; ibid., 5865). Aminimide-derived carbohydrate mimetics may be synthesized from carbohydrate derivatives containing functional groups, such as epoxide groups, ester groups, hydrazine groups or alkylating groups, which are compatible with the aminimide forming and catenating reactions outlined above, thus allowing the carbohydrates to be attached to a basic scaffold, or to be arrayed along a backbone in a precise controlled manner. Examples for the synthesis of such carbohydrate derivatives are outlined below.

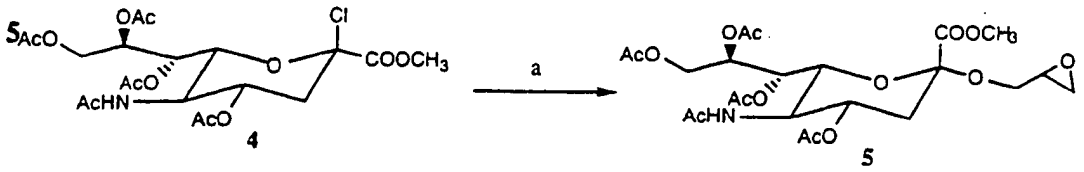
Carbohydrate mimetics-synthesis of aminimide containing molecules

Scheme 1



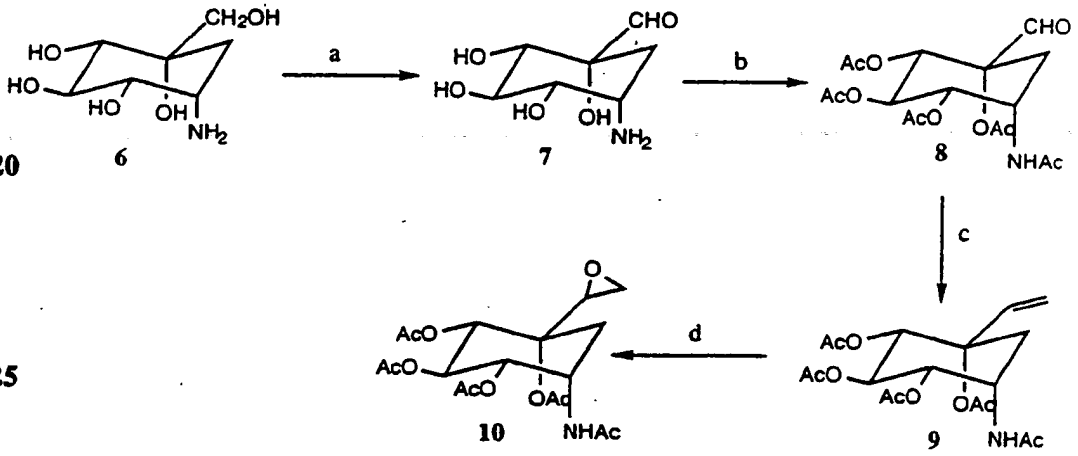
(a) p-TsCl (1 eq), Pyridine, rt
(b) DBU, diethyl ether, rt
(c) Ac_2O, Pyridine, CH_2Cl_2, rt

Scheme 2



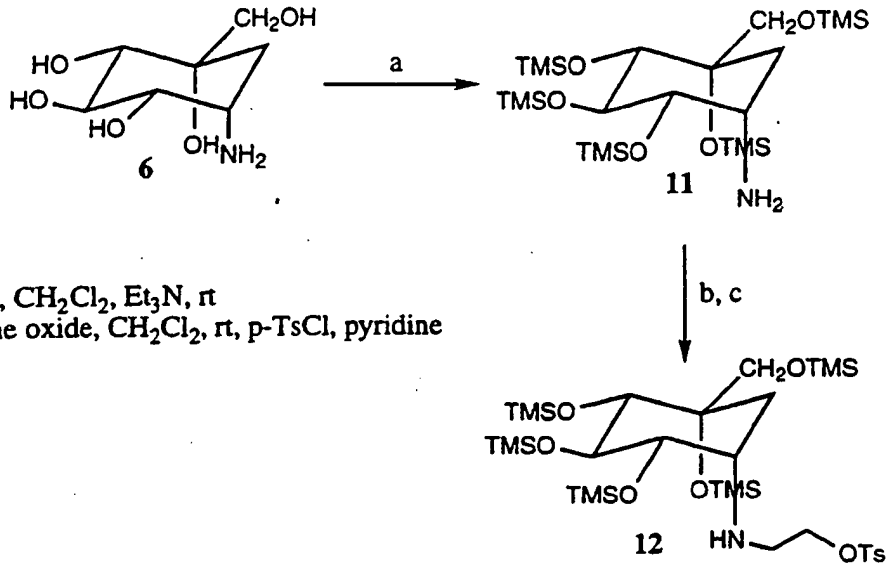
(a) Glycidol, Ag-Salicylate, C_6H_6, rt

Scheme 3



(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C
(b) Ac_2O, Pyridine, CH_2Cl_2, rt
(c) Ph_3PCH_2I, PhLi, THF, rt
(d) m-CPBA, CH_2Cl_2, rt

Scheme 4



(a) TMSCl, CH_2Cl_2, Et_3N, rt
(b) Ethylene oxide, CH_2Cl_2, rt, p-TsCl, pyridine

4.4.6 Synthesis of Pharmacophore Mimetics

Background

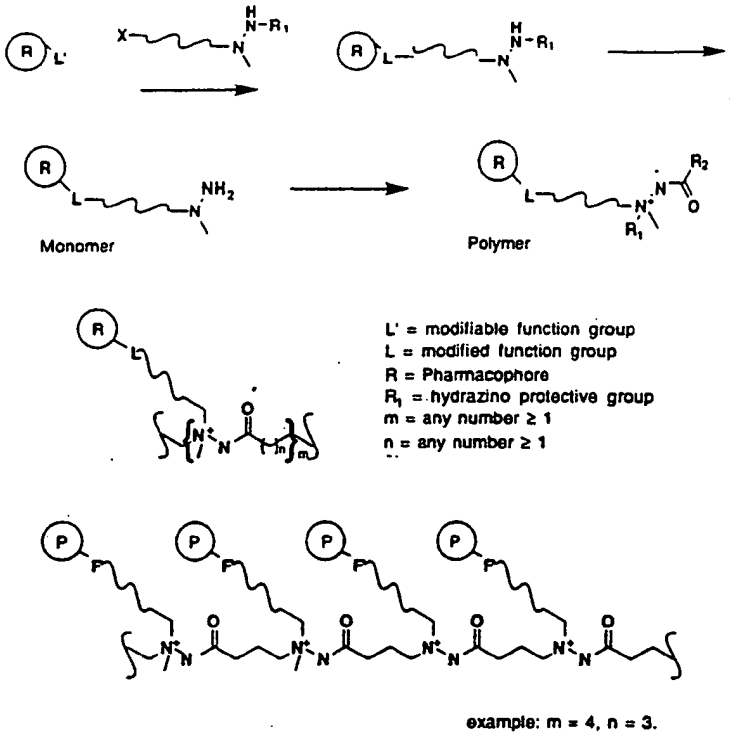
The physical principle governing the binding of a natural ligand or substrate to a receptor or active site of an enzyme, nucleotide or carbohydrate are the same principles governing the binding of non-peptide, non-nucleotide and non-carbohydrate compounds (competitive inhibitors or agonists). The modification of a known biologically active compound as a lead or prototype, then synthesizing and testing its structural congers, homologues or analogues is a basic strategy for the development of new therapeutic agents. Several advantages of this method are:

- Greater probability of theses modified derivatives to possess physiological properties most similar to those of the prototype than those tested at random.
- Possibility of obtaining pharmacologically superior agents.
- Economical production of a new drug.
- Structure-activity relationships can be established to assist in further developments.

The objectives of any drug discovery program are: (a) to obtain drugs that have more desirable properties than the prototype in potency, specificity, stability, pharmalogical duration, toxicity, ease of administration and cost of production; (b) the discovery of features of the molecule which impart pharmalogical action. The term pharmacophore is used to describe these key features that impart this pharmalogical action.

Several technologies exist where a biologically active compound, for example a protein or polypeptide, is attached to a solid support, such as a resin or glass surface. These linked compounds show diverse inhibitory activity, an indication that linked molecules are able to retain their binding properties despite the partial loss of mobility.

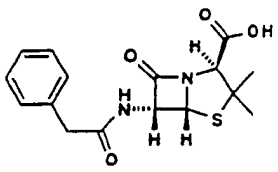
There are a wide variety of general pharmacophores known which display specific known modes of activity, e.g., ß-lactam actibacteric, interfering with bacterial cell wall; piperidine and peperizine, which can act as psychotropic agents or anticholinergics; and xanthines as stimulants. The following general schemes outline the synthesis of pharmacophore molecules, for inclusion in the various aminimide polymer backbone. The following scheme outlines the general approach:



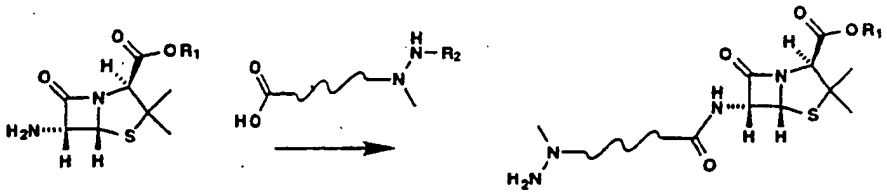
The polymer can be arranged so as to be homogeneous, that is, the entire polymer is made from the same monomers, or heterogeneous, that is, the polymer can be made with any varying sequences of monomers in a controllable fashion. The length of the linker, the molecular fragment that connects the pharmacophoric portion to the quatenary nitrogen of the aminimide polymer, can be of various lengths and shapes, such as but not limited to a linear alkyl chain. As such, the arrangement and the geometric configuration of the pharmacophores on the backbone polymer can be controlled.

The following figures are general examples of pharmacophores that are illustrative of the approach:

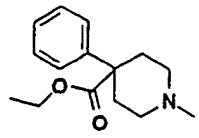
Antibacterials, e.g.,



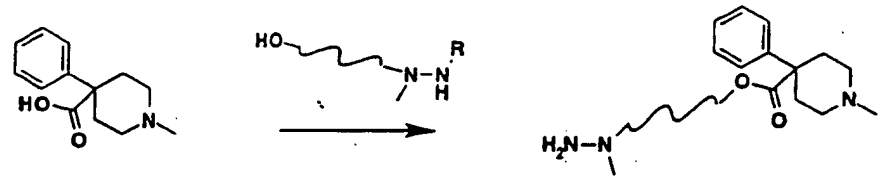
Benzylpenicillin



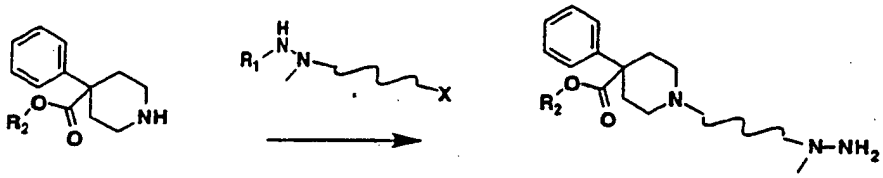
Analgesics/Antispasmodics/Psychotropics, e.g.,



Meperidine



or



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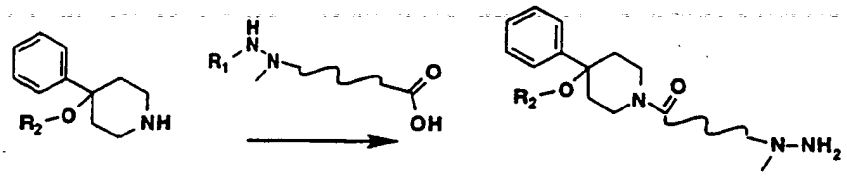
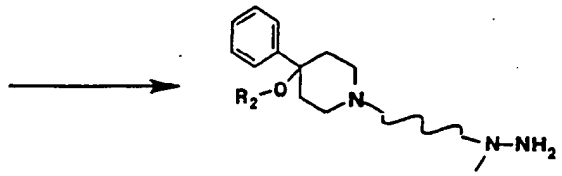
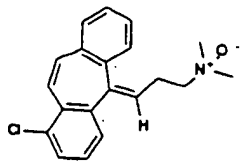
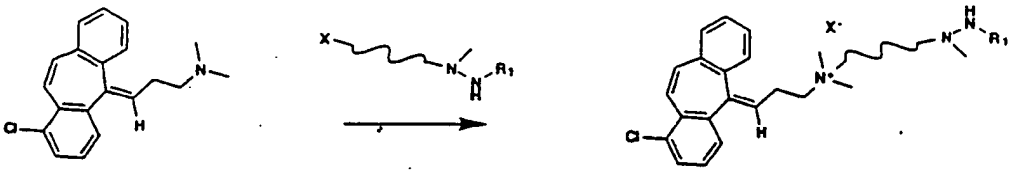




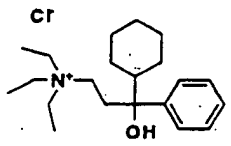
Antidepressants, e.g.,



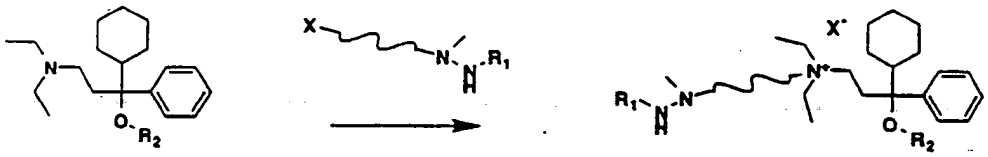
Benzaprinoxide



Anticholinergics, e.g.,



Tridihexethyl Chloride



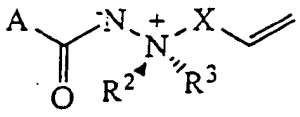
4.4.7 Synthesis and Polymerization of Chiral Aminimide-Containing Monomers

The conversion of many of the aminimide structures described above into monomer building blocks which can be polymerized to give novel macromolecules, which are useful in a variety of high technological applications, is contemplated. The following synthetic approaches are expected to be very useful in the production of new materials.

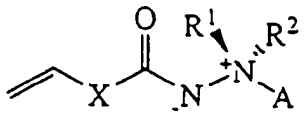
(a) Free-Radical Polymerization of Vinyl Aminimides

Chiral (as well as achiral) vinylaminimide monomers of the general structures shown below may be readily prepared, following the procedures outlined above, and

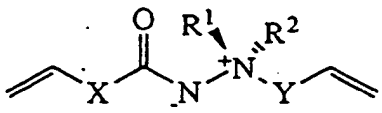
used in free-radical polymerizations, according to experimental procedures well-known in the art, to produce a vast array of novel polymeric materials.



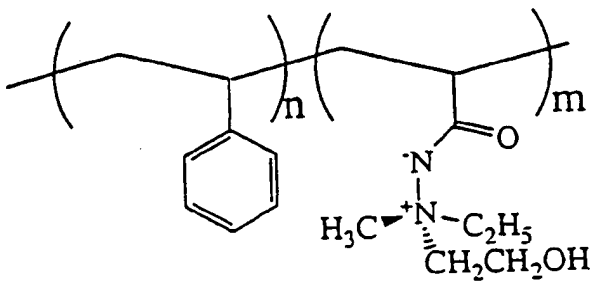
and



Additional monomeric structures useful in preferred free radical polymerizations include those shown below; they produce polymeric chains capable of being crosslinked into more rigid structures. The monomers shown below may be prepared using the synthetic procedures outlined above, and the polymerization/crosslinking reactions may be run using standard polymerization techniques. See, for example, Practical Macromolecular Organic Chemistry, Braun, Cherdron and Kern, trans. by K. Ivin, 3ed., Vol Z, Harwood Academic Publishers, New York, N.Y. 1984.

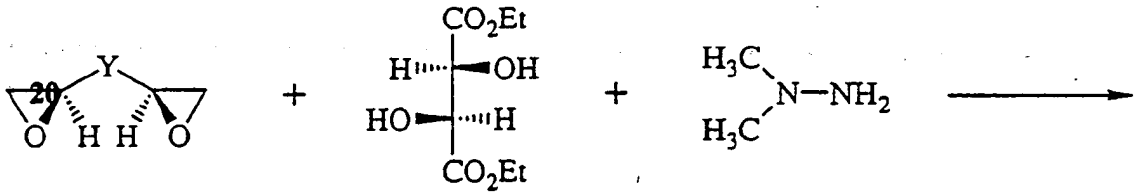


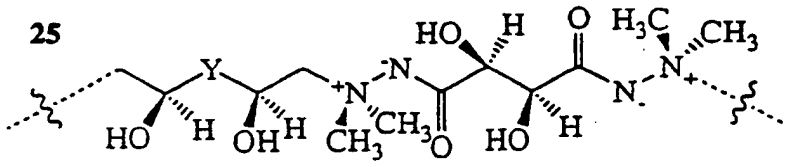
The monomers shown above may be polymerized with other alkenes or dienes, which are either commercially available or readily prepared using standard synthetic reactions and techniques, to furnish copolymers with novel structures and molecular recognition characteristics.



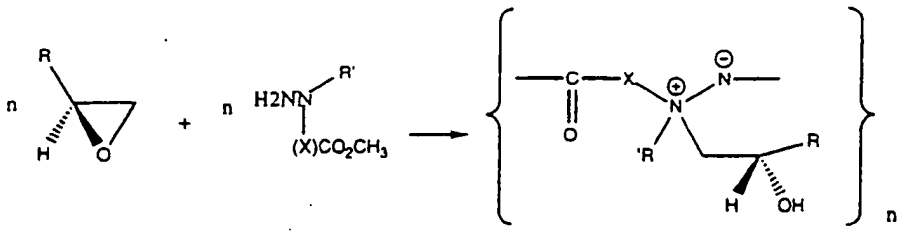
(b) Condensation Polymerizations Producing Aminimide-Containing Macromolecules

Sequential condensations of aminimide-forming molecules may be used to produce a variety of novel polymers of controlled size. An example involving dimeric epoxides and esters is given below; processes involving trimeric and more complex epoxides and esters are also contemplated; and experimental conditions for running these polymerizations (including techniques for resolving experimental difficulties as product molecular weight increases) have been described above.





Alternatively, condensation polymerization may be carried out by reacting alpha carboxyester derivatized hydrazines (prepared as outlined above) with chiral epoxides to produce the novel polymers shown:

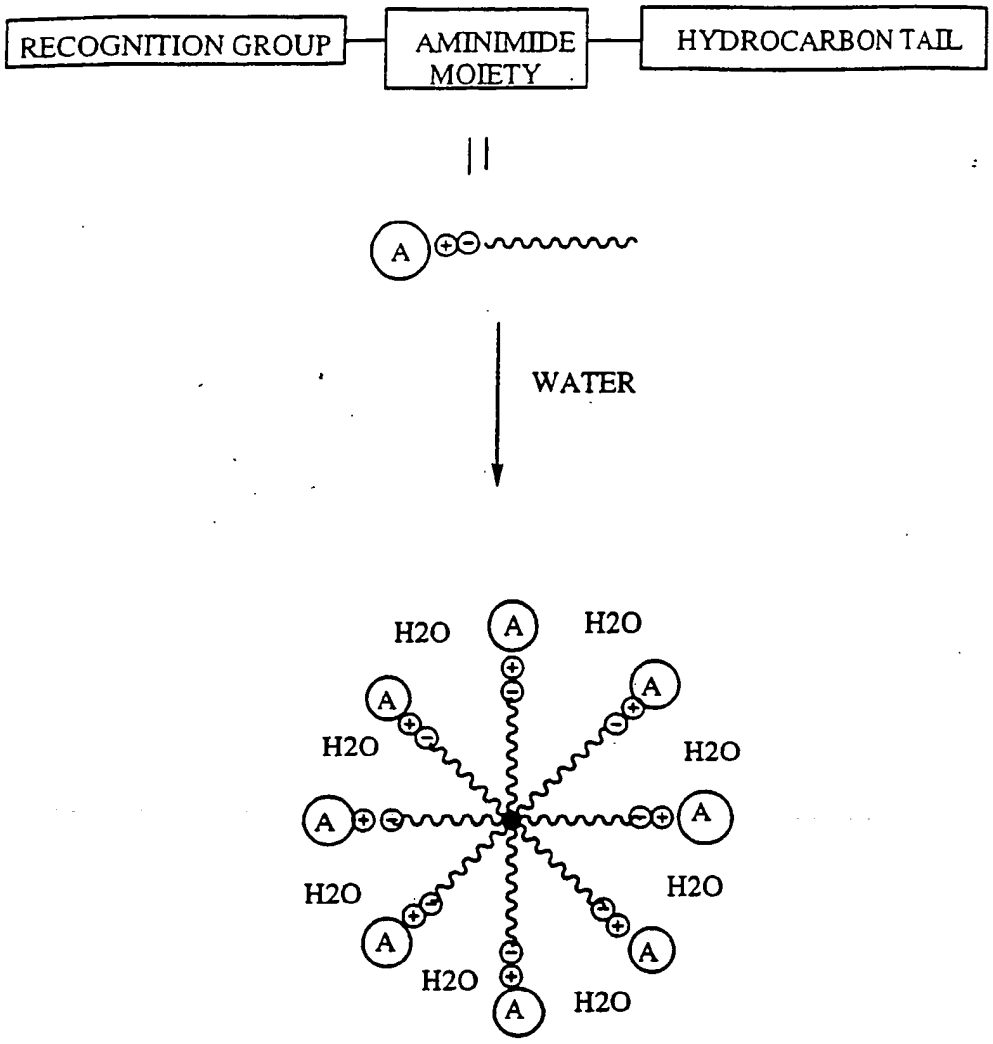


When the polymerization reaction is carried out with molecules immobilized on a support, e.g. silica, a support capable of specific molecular recognition is produced; an example of such a support is given below:

FORMULA 88
#4, p. 82

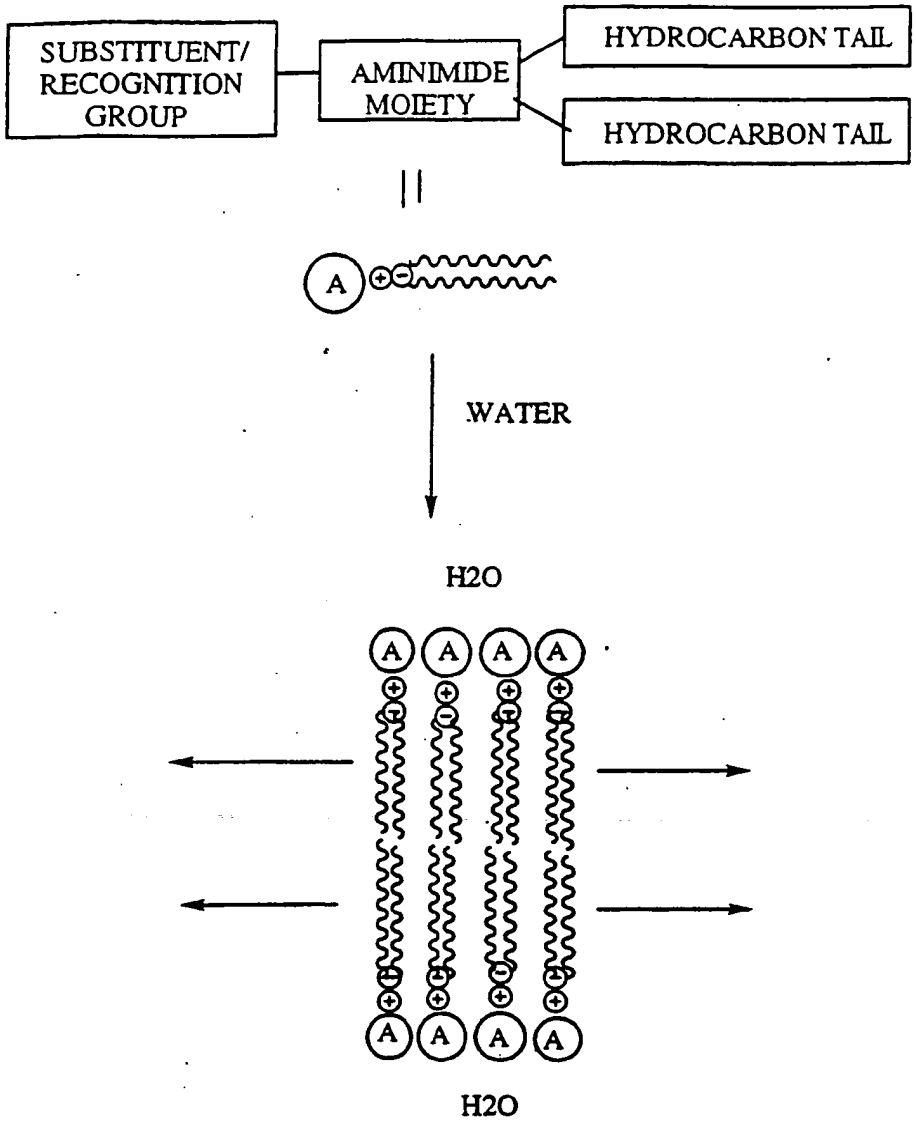
4.4.8 Lipid Mimetics

Aminimide conjugate structures containing a single long-chain hydrocarbon group can be used as amphiphillic surface active materials which have great utility as delivery systems for the administration of drugs. The attachment of a "recognition group" to the aminimide moiety gives a material which is highly compatible with lipophillic structures, such as cell wall membranes, and which itself will form micellular structures in water with the recognition group pointed out or "displayed " on the surface of the micelle. This may be represented by the general schematic shown:



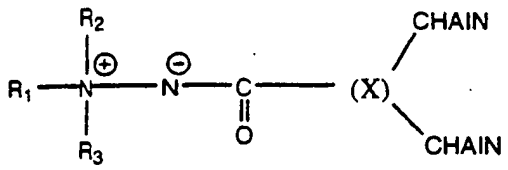
Examples of the synthesis of these conjugates are given below.

Aminimide structures possessing two long-chain alkyl groups capable of producing bilayer membrane structures are preferred embodiments of the present invention. Because of the presence of the double tail on the amphiphilic group, these molecules prefer to form continuous bilayer membrane structures, such as those found in cell wall membranes rather than micelles. As such they may function as "cell wall-mimicking" components. This is schematically illustrated below:

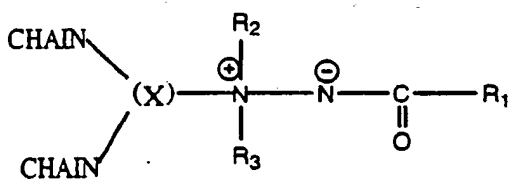


Among the many uses for these unique compounds are the isolation and stabilization of biologically-active molecules from the cell-wall, the construction of affinity chromatography supports for the isolation and purification of amphiphilic macromolecules, e.g., receptors, enzymes, etc., and the effective delivery-administration of drugs.

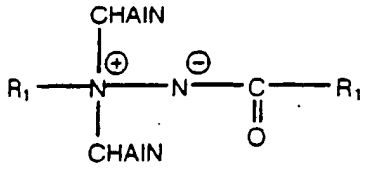
The structure of one preferred lipid mimetic is shown below. Substituents R may be chosen from a variety of structures of various sizes including structures of ligands of biological receptors or enzymes; a preferred combination of substituents involves sterically small groups for R1 and R2 and a group such as A or B described above for R3; the long-chain alkyl groups are 4-30 carbons in length; group X is a linker composed of atoms chosen from the set of C, H, N, O, S, P and Si.



A further desirable variation of the surface-active structure shown above is as follows:



In the above structure, X is a linker group (e.g., CH); one or more substituents R are chosen from the group of structures A and B described above and the remaining substituent(s) in preferably a sterically small group, e.g., H, or CH3. An additional desirable amphiphilic structure is shown below; substituent structures are similar to those listed above.



Lipid mimetics are illustrated in the Examples that follow.

4.4.9 Fabrication of Aminimide-Containing Macromolecular Structures Capable of Specific Molecular Recognition

In an embodiment of the invention aminimide molecular building blocks may be utilized to construct new macromolecular structures capable of recognizing specific molecules ("intelligent macromolecules"). The "intelligent macromolecules" may be represented by the following general formula:

P - C - L - R

where, R is a structure capable of molecular recognition;

L is a linker;

P is a macromolecular structure serving as a supporting platform;

C is a polymeric structure serving as a coating which surrounds P.

Structure R may be a native ligand or a biological ligand-acceptor or a mimetic thereof, such as those described above.

Linker L may be a chemical bond or one of the linker structures listed above, or a sequence of subunits such as amino acids, aminimide monomers, oxazolone-derived chains of atoms, etc.

Polymeric coating C may be attached to the supporting platform either via covalent bonds or "shrink wrapping," i.e. the bonding that results when a surface is subjected to coating polymerization is well known to those skilled in the art. This coating element may be

1) a thin crosslinked polymeric film 10 - 50 Angstroms in thickness;

2) a crosslinked polymeric layer having controlled microporosity and variable thickness, or

3) a controlled microporosity gel. When the support platform is a microporous particle or a membrane, as described below, the controlled microporosity gel may be engineered to completely fill the porous structure of the support platform. The polymeric coatings may be constructed in a controlled way by carefully controlling a variety of reaction parameters such as the nature and degree of coating crosslinking, polymerization initiator, solvent, concentration of reactants, and other reaction conditions, such as temperature, agitation, etc., in a manner that is well known to those skilled in the art.

The support platform P may be a pellicular material having a diameter (dp) from 100 Angstroms to 1000 microns, a latex particle (dp 0.1 - 0.2 microns), a microporous bead (dp 1 - 1000 microns), a porous membrane, a gel, a fiber, or a continuous macroscopic surface. These may be commercially available polymeric materials, such as silica, polystyrene, polyacrylates, polysulfones, agarose, cellulose, etc. or synthetic aminimide-containing polymers such as those described below.

Any of the elements P, C, L, or R containing an aminimide-based structure is derived from a form of the element containing a precursor to the aminimide-based structure. The multisubunit recognition agents above are expected to be very useful in the development of targeted therapeutics, drug delivery systems, adjuvants, diagnostics, chiral selectors, separation systems, and tailored catalysts.

In the present specification the terms "surface", "substrate", and "structure" refer to either P, P linked to C or P linked to C and L as defined above.

Thus, another aspect of the invention relates to a three-dimensional crosslinked random copolymer containing, in copolymerized form about 1 to 99 parts of a free-radically

polymerizable monomer containing an aminimide group; up to 98 parts of a free-radically addition-polymerizable comonomer; and about 1 to 50 parts of at least one crosslinking monomer.

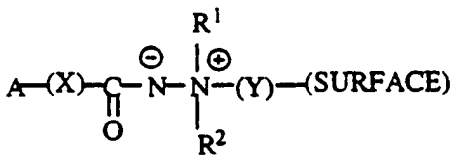
The comonomer used in this copolymer may be water-soluble or water-insoluble, and the copolymer is fashioned into a water-insoluble bead, a water-insoluble membrane or a latex particle, or can be a swollen aqueous gel suitable for use as an electrophoresis gel.

This copolymer is preferably the reaction product of about 1 to 99 parts of a condensation-polymerizable monomer containing a moiety cluster selected from the group consisting of (1) at least three epoxy groups, (2) at least three ester groups, (3) at least one epoxy and at least two ester groups and (4) at least one ester and at least two epoxy groups; about 1 to 99 parts of a second condensation-polymerizable monomer containing a moiety cluster selected from the group consisting of (1) at least two ester groups, (2) at least two epoxy groups and (3) at least one ester and one epoxy group; and an amount of 1,1-dialkylhydrazine equivalent, on a molar basis, substantially equal to the total molar content of epoxy groups.

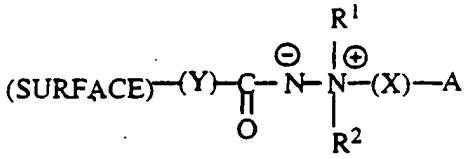
4.4.9.1 Aminimide Containing Support Materials

Commercially available or readily obtainable chromatographic support materials for chromatographic and other applications, as well as other fabricated materials can be derivatized with tailored aminimide moieties, through chemical modification, producing novel materials capable of recognizing specific molecular structures.

These are represented by the following general structures:

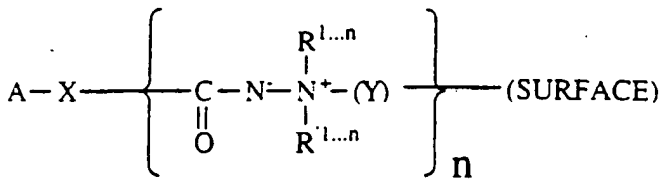


and

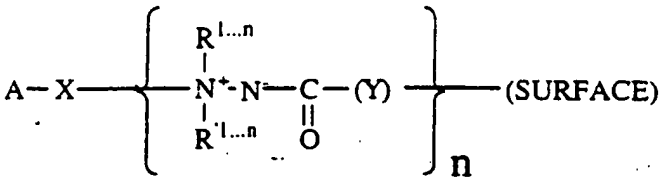


In the structures above, A is selected from the group consisting of amino acids, oligopeptides, polypeptides and proteins, nucleotides, oligonucleotides, polynucleotides, carbohydrates, molecular structures associated with therapeutic agents, metabolites, dyes, photographically active chemicals, and organic structures having desired steric, charge, hydrogen-bonding or hydrophobicity elements; X and Y are chemical bonds or groups consisting of atoms selected from the set of C, H, N, O, S; R1 and R2 are chosen from the group of alkyl, carbocyclic, aryl, aralkyl, alkaryl and, preferably, structures mimicking the side-chains of naturally-occurring amino acids.

Surfaces and other structures functionalized with multiple aminimide subunits are also preferred; general structures are shown below.



+

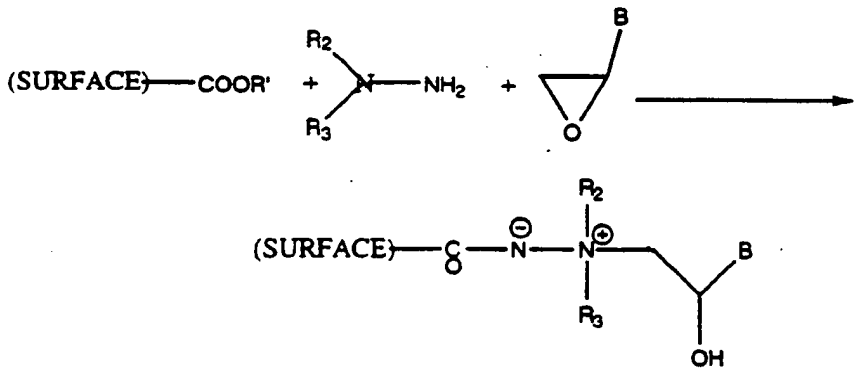


In the above structures R1...n and R'1...n are used to illustrate the manner in which the hydrazine substituents R1 and R2 can be varied in each polymerization step described above to produce a functional supported oligomer or polymer.

The following chemical modifications can be used to prepare aminimide-functionalized surfaces.

4.4.9.1.1 Functionalization of Ester and Epoxy Surfaces

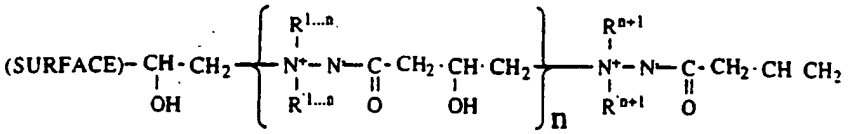
A surface bearing ester groups can be treated with an epoxide, containing desired group B, and a disubstituted hydrazine to form an aminimide surface as follows:



To carry out the above reaction, the surface is treated with a solution containing a 10% molar excess of the epoxide (based on the calculated number of reactive ester groups of the surface), and a stoichiometric amount of the hydrazine (with respect to the amount of the epoxide) in an appropriate solvent, such as an alcohol, with shaking. The mixture is then allowed to stand at room temperature for 1 week with occasional shaking. At the end of this period, the solvent is removed by decantation, and the surface is thoroughly washed with fresh solvent and air dried.

This approach allows the functionalization of readily available supports containing ester groups.

The above reaction sequence can also be employed with an epoxide-functionalized surface:

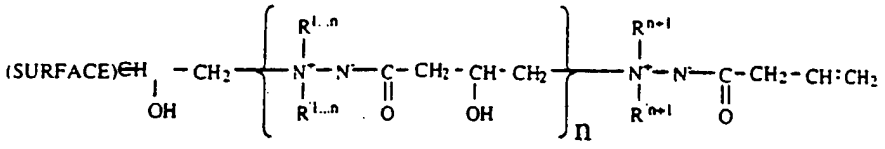


To carry out the above reaction, the surface is treated with a solution containing a 10% molar excess of the ester (based on the calculated number of reactive epoxide groups of the support), and a stoichiometric amount of the hydrazine (with respect to the amount of the ester used), in an appropriate solvent, such as an alcohol, with shaking. The mixture is then allowed to stand at room temperature for 1 week with occasional shaking. At the end of this period, the solvent is removed by decantation, and the surface is thoroughly washed with fresh solvent and air dried.

The foregoing reaction can be modified by utilizing an ester whose substituent B contains a double bond. After completion of the reaction shown above, the double bond of the ester can be epoxidized using one of a variety of reactions including the asymetric epoxidation of Sharples (e.g., utilizing a peracid under suitable reaction conditions well-known in the art), and the product used as the epoxide in a new repetition of

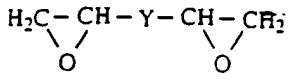
the aminimide-forming reaction. The overall process can be repeated to form oligomers and polymers.

For example, using ß-butenoic acid methyl ester as the ester, n repetitions of the above reaction sequence produces a compound of the form:

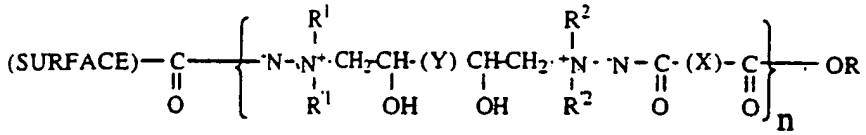


where the designations R2...n and R3...n are used to illustrate the manner in which the hydrazine substituents R2 and R3 are varied in each polymerization step, if desired, to produce an oligomer or polymer.

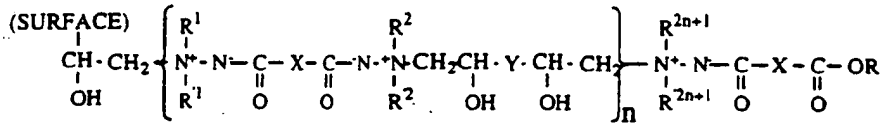
The foregoing reactions can be carried out using bifunctional esters of the form ROOC-X-COOR', where X is a linker and R and R' are alkyl groups as defined above, and/or bifunctional epoxides of the form shown below,



wherein Y is a linker as defined above, to form desirable polymers. If an ester-functionalized surface is reacted with bifunctional esters and epoxides, the resulting surface will have the following general structure.

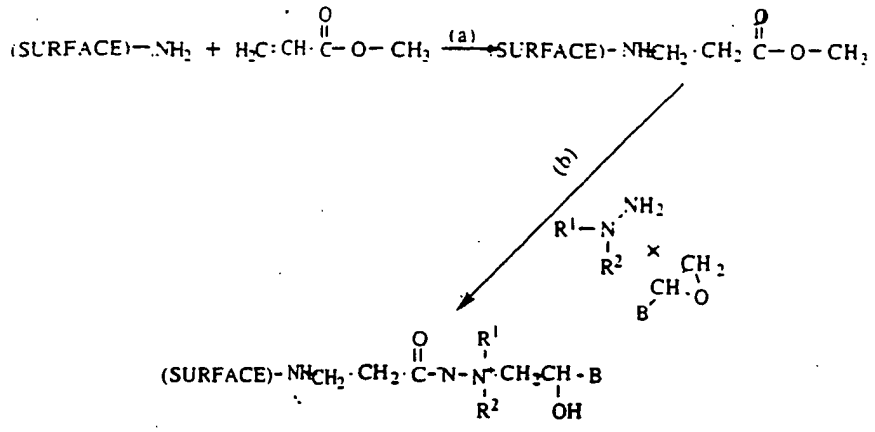


If an epoxide-functionalized surface is reacted as above the derivatized surface will have the following general structure.



4.4.9.1.2 Functionalization of Amine Surfaces

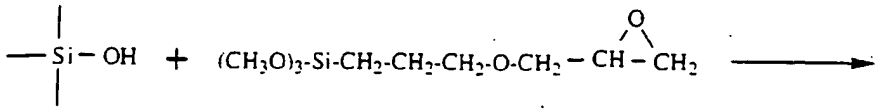
An amine-functionalized surface can be converted to an ester-bearing surface by reaction with an acrylic ester as shown in sequence (a) below. This reaction is followed by reaction with hydrazine and an epoxide as shown in sequence (b).

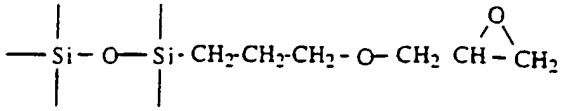


For reaction (a), a 10% molar excess of methyl acrylate (based on the number of reactive amino groups the surface as determined by a titration with acid) is dissolved in an appropriate solvent, such as an alcohol, and added to the surface. After addition is complete, the mixture is shaken at room temperature for 2 days. The solvent is then removed by decantation and the surface is washed thoroughly with fresh solvent in preparation for the next step.

For reaction (b) the stoichiometric amount of a 1:1 mixture of the hydrazine and the epoxide, is combined in an appropriate solvent, such as an alcohol, and quickly added to the solvent-wet surface from reaction (a). The mixture is shaken at room temperature for 3 days. The solvent is then removed by decantation, and the surface is washed thoroughly with fresh solvent and dried.

The above reaction sequence can also be employed with an epoxide-functionalized surface, in which case substituent B in the structure above represents the surface and the desired functional group bears the amine moiety. One way of obtaining such a surface is to react a silica surface with a silicic ester containing an epoxide group to produce a so-called "epoxy silica", as shown below.

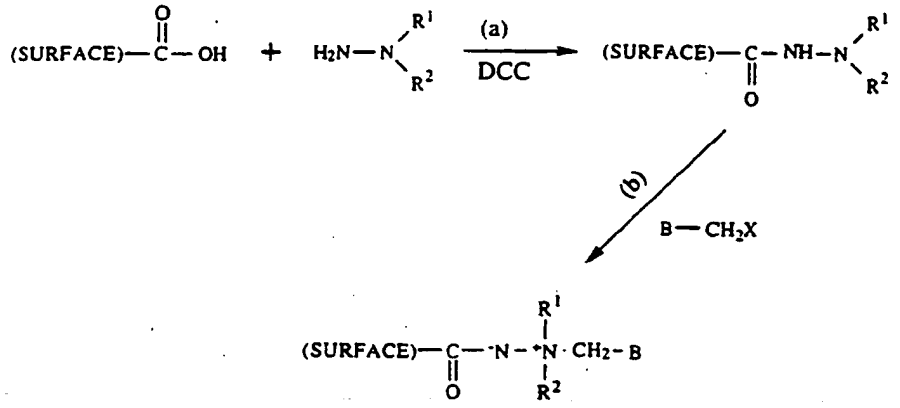




("Epoxy Silica")

4.4.9.1.3 Functionalization of Carboxylic-Acid-Containing Surfaces

A surface functionalized with a carboxylic acid group can be reacted with an 1,1-dialkylhydrazine and a coupling agent, such as dicyclohexyl carbodiimide (DCC), to form a hydrazone-containing surface as shown in step (a) below. This surface can then be coupled with a desired group B bearing a substituent capable of alkylating the hydrazone to give an aminimide structure (after treatment with base), as shown in step (b):



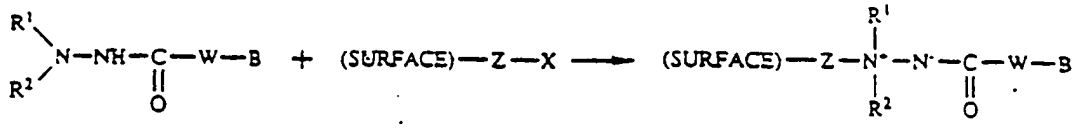
Substituent B is a surface functionalized with an alkylating agent capable of reacting with a hydrazone.

To perform the above chemical modification of a carboxyl-bearing surface, the surface is treated with a 10% molar excess equimolar amounts of the N,N-dimethylhydrazine and DCC in a suitable solvent, such as methylene chloride, and the mixture is shaken for 2 hours at room temperature. The slurry is then removed by decantation and the surface is washed thoroughly with fresh solvent to remove any residual precipitated dicyclohexyl urea. The surface is then treated with a stoichiometric amount of the alkylating agent in a suitable solvent, warmed to 70 _C and held at this temperature for 6 hours. The mixture is then cooled, the solvent is removed

by decantation, and the surface is washed with fresh solvent and dried.

4.4.9.1.4 Funtionalization of Surfaces Capable of Hydrazide Alkylation

A surface bearing a group capable of alkylating acyl hydrazones can be functionalized to contain aminimide groups as follows:

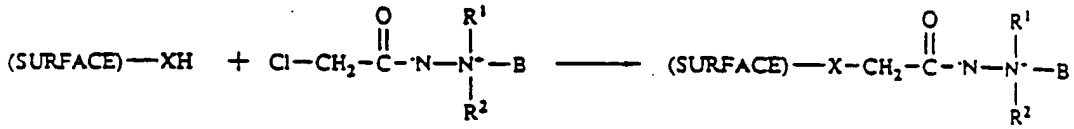


In the equation above, Z and W are linkers composed of atoms selected from the set of C, N, H, O, S, and X is a suitable leaving group, such as a halogen or tosylate.

A hydrazone bearing a desired group B is produced by reacting the appropriate 1,1'-dialkylhydrazine with any of a variety of derivatives containing B via reactions that are well-known in the art. These derivatives may be acid halides, azlactones (oxazolones), isocyanates, chloroformates, or chlorothioformates.

4.4.9.1.5 Functionalization of Surface Bearing -NH, -SH, or -OH Groups with Chloromethyl Aminimides

Surfaces functionalized with -NH2, -SH, or -OH groups can be functionalized by treating them with chloromethyl aminimides in the presence of strong base using the experimental conditions outlined above:

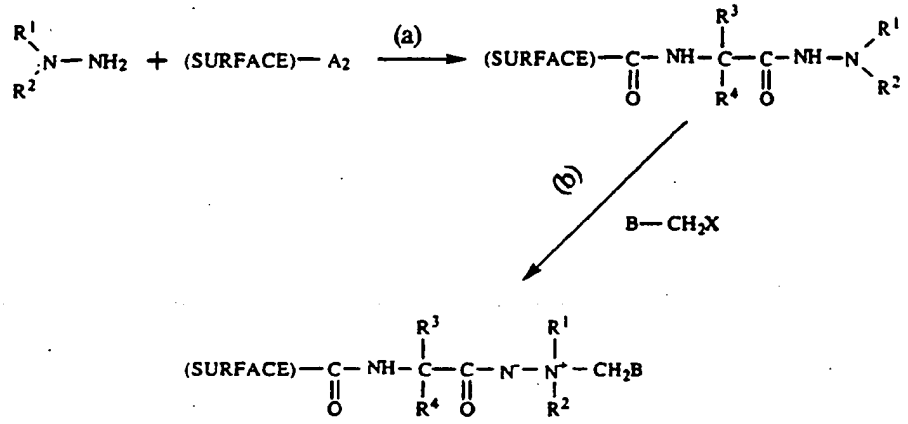


The required chloromethyl aminimides can be prepared by known literature procedures (See, e.g., 21 J.

Polymer Sci., Polymer Chem. Ed. 1159 (1983)), or by using the techniques described above.

4.4.9.1.6 Functionalization of Oxazolone-Containing Surfaces

Oxazolone-containing surfaces can be functionalized by first reacting them with 1,1'-dialkylhydrazine as shown in step (a) below followed by alkylation of the resulting hydrazone with an alkylating agent B-CH2-X as shown in step (b); reaction conditions similar to those described above are expected to be effective in carrying out these modifications.



In the structures above, R3 and R4 are derived from the five membered azlactone ring denoted by Az.

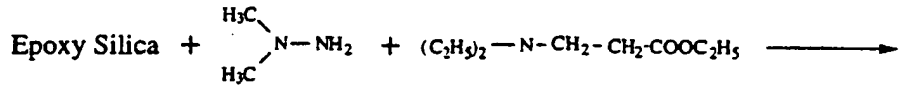
Although the previous discussions are specically directed to the functionaliziation of surfaces, these reactions can also be used to construct aminamide linkages to the other speciesof A and B which are described in this application.

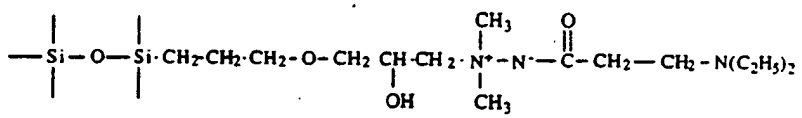
4.4.10 Preparation of Aminimide-Based Coatings for Support Materials

It is possible to produce aminimide-functionalized composite support materials by coating various soluble aminimide formulations on the surfaces of existing supports,

and subsequently crosslinking the resulting coatings in place to form mechanically stable surfaces. The coating may be engineered for a particular application (e.g., to take the form of a thin non-porous film or to possess localized microporosity for enhanced surface area) by judicious selection of process conditions, monomer loading levels, the crosslinking mechanism and the amount of crosslinker.

For example, any of the foregoing reactions can be carried out with a vinyl aminimide in contact with a selected surface, which is polymerized according to well-known techniques (see, e.g., U.S. Patent No. 4,737,560). The polymerization results in a surface coated with a polymer containing aminimide side-chains. Other coating procedures employing aminimide functional groups are described below in greater detail.





4.4.11 Synthesis of Aminimide-Containing Materials Via Polymerizations of Aminimide-Based Molecules

In addition to utilizing aminimide chemistry to chemically modify commercially available or readily obtainable surfaces, new surfaces and other materials can be fabricated de novo from aminimide precursors bearing polymerizable groups by polymerizations and/or copolymerizations in the presence or absence of crosslinking agents. Depending upon the properties for the desired material, various combinations of monomers, crosslinkers, and ratios thereof may be employed. The resultant support materials may be latex particles, porous or non-porous beads, membranes, fibers, gels, electrophoresis

gels, or hybrids thereof. Furthermore, the monomers and crosslinking agents may or may not all be aminimides.

Vinyl or condensation polymerizations may be advantageously employed to prepare the desired aminimide-containing materials. Vinyl polymerization can include use of one or more monomers of the form CH2=CH-X that are copolymerizable with aminimides; suitable examples include styrene, vinyl acetate, and acrylic monomers. If desired, compatible non-aminimide crosslinkers, such as divinyl benzene, may be employed (either singly or in combination as the other such agents).

Condensation polymerization may be accomplished using multifunctional epoxides and multifunctional esters with the appropriate amounts of an 1,1'-dialkylhydrazine, using the reaction conditions described above. Either the ester component or the epoxide component should be at least trifunctional to obtain three-dimensionally crosslinked polymer structures; preferably, both components are trifunctional.

The nature and conditions of processing, the ratio of the various monomers and the ratio of crosslinker to total monomer content can be varied to produce a variety of product structures (e.g., beads, fibers, membranes, gels, or hybrids of the foregoing) and to tailor the mechanical and surface properties of the final product (e.g., particle size and shape, porosity, and surface area). Appropriate parameters for a particular application are readily selected by those skilled in the art.

4.4.12 Combinatorial Libraries of Peptidomimetics Derived From Aminimide Modules

The synthetic transformations of aminimides outlined above may be readily carried out on solid supports in a manner analogous to performing solid phase peptide synthesis, as described by Merrifield and others (see for example, Barany, G., Merrifield, R.B., Solid Phase Peptide

1-284, Acad. Press, New York 1980; Stewart, J.M., Yang, J.D. Solid Phase Peptide Synthesis, 2nd ed., Pierce Chemical Co., Rockford, Illinois 1984; Atherton, E., Sheppard, R.C., Solid Phase Peptide Synthesis, D. Rickwood & B.D. Hames eds., IRL Press ed. Oxford U. Press, 1989). Since the assembly of the aminimide-derived structures is modular, i.e., the result of serial combination of molecular subunits, huge combinatorial libraries of aminimide-based oligomeric structures may be readily prepared using suitable solid-phase chemical synthesis techniques, such as those of described by Lam (K.S. Lam, et al. Nature 354, 82 (1991)) and Zuckermann (R.N. Zuckermann, et al., Proc. Natl. Acad. Sci. USA, 89, 4505 (1992); J.M. Kerr, et al., J. Am Chem. Soc., 115, 2529 (1993)). Screening of these libraries of compounds for interesting biological activities, e.g., binding with a receptor or interacting with enzymes, may be carried out using a variety of approaches well known in the art. With "solid phase" libraries (i.e., libraries in which the ligand-candidates remain attached to the solid support particles used for their synthesis) the bead-staining technique of Lam may be used. The technique involves tagging the ligand-candidate acceptor (e.g., an enzyme or cellular receptor of interest) with an enzyme (e.g., alkaline phosphatase) whose activity can give rise to color production thus staining library support particles which contain active ligand-candidates and leaving support particles containing inactive ligand-candidates colorless. Stained support particles are physically removed from the library (e.g., using tiny forceps that are coupled to a micromanipulator with the aid of a microscope) and used to structurally identify the biologically active ligand in the library after removal of the ligand acceptor from the complex by e.g., washing with 8M guanidine hydrochloride. With "solution-phase" libraries, the affinity selection techniques described by Zuckermann above may be employed.

An especially preferred type of combinatorial library is the encoded combinatorial library, which involves the synthesis of a unique chemical code (e.g., an oligonucleotide or

peptide), that is readily decipherable (e.g., by sequencing using traditional analytical methods), in parallel with the synthesis of the ligand-candidates of the library. The structure of the code is fully descriptive of the structure of the ligand and used to structurally characterize biologically active ligands whose structures are difficult or impossible to elucidate using traditional analytical methods. Coding schemes for construction of combinatorial libraries have been described recently (for example, see S. Brenner and R.A. Lerner, Proc. Natl. Acad. Sci. USA , 89, 5381 (1992); J. M. Kerr, et al. J. Am. Chem. Soc. 115, 2529 (1993)). These and other related schemes are contemplated for use in constructing encoded combinatorial libraries of oligomers and other complex structures derived from aminimide units.

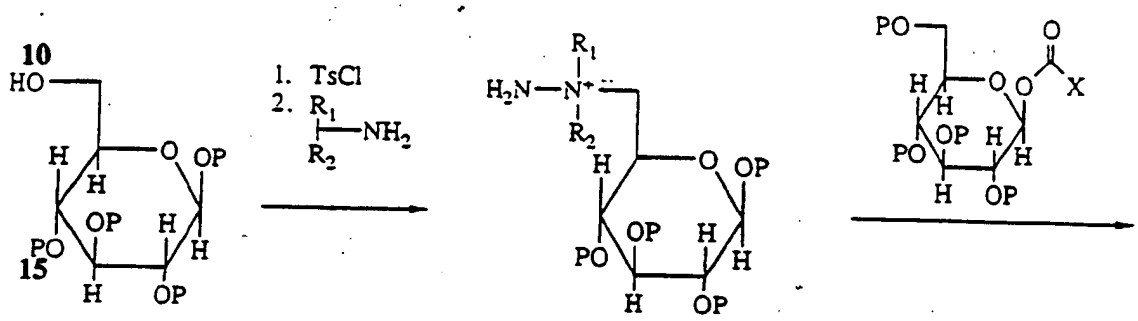
The power of combinatorial chemistry in generating screenable libraries of chemical compounds e.g., in connection with drug discovery, has been described in several publications, including those mentioned above. For example, using the "split solid phase synthesis" approach outlined by Lam et al., the random incorporation of 20 different aminimide units into pentameric structures, wherein each of the five subunits in the pentamer is derived from one of the aminimide units, produces a library of 205 = 3,200,000 peptidomimetic ligand-candidates, each ligand-candidate is attached to one or more solid-phase synthesis support particles and each such particle contains a single ligand-candidate type. This library can be constructed and screened for biological activity in just a few days. Such is the power of combinatorial chemistry using aminimide modules to construct new molecular candidates.

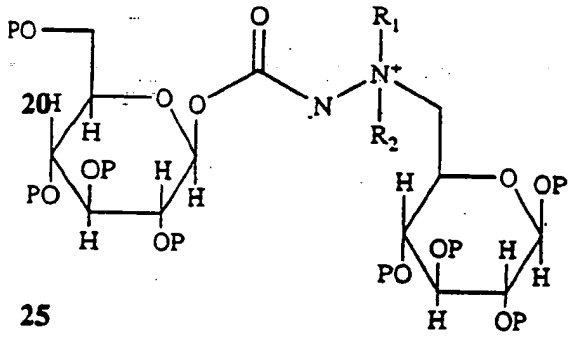
An example of one of the many methods for use in constructing random combinatorial libraries of aminimides-based compounds; the random incorporation of three aminimides derived from alpha-chloroacetyl chloride and the hydrazines shown below to produce 27 trimeric structures linked to the support via a succinoyl linker is given below.

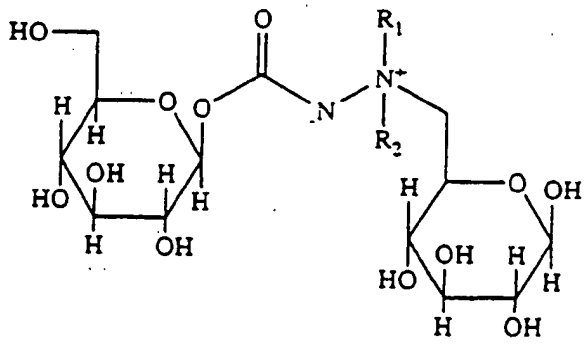
4.4.13 Design and Synthesis of Aminimide-Based Glycopeptide Mimetics

A great variety of saccharide and polysaccharide structural motifs incorporating aminimide structures are contemplated including, but not limited to, the following.

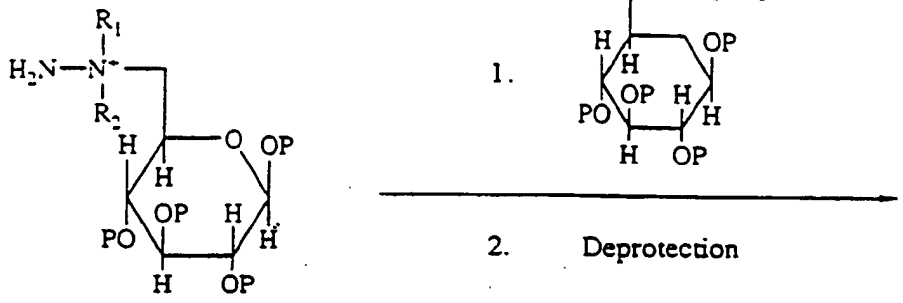
(1) Replacement of certain glycosidic linkages by aminimide backbones using reactions well known in the art of

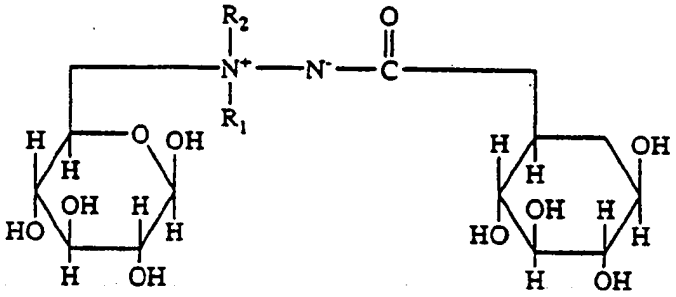






(2) Use of aminimide structures as linkers holding in place a sugar derivative and a tailored mimetic, or another sugar.



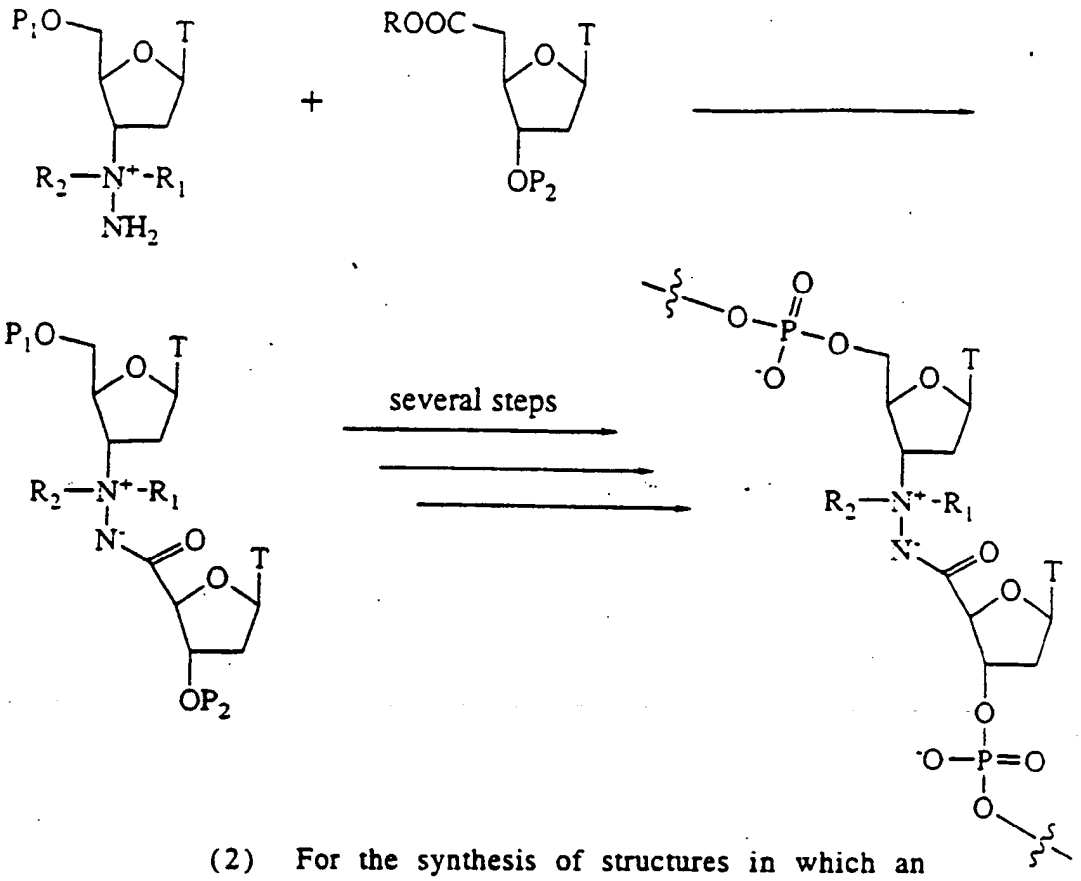


4.4.14 Design and Synthesis of Aminimide-Containing Oligonucleotide Mimetics

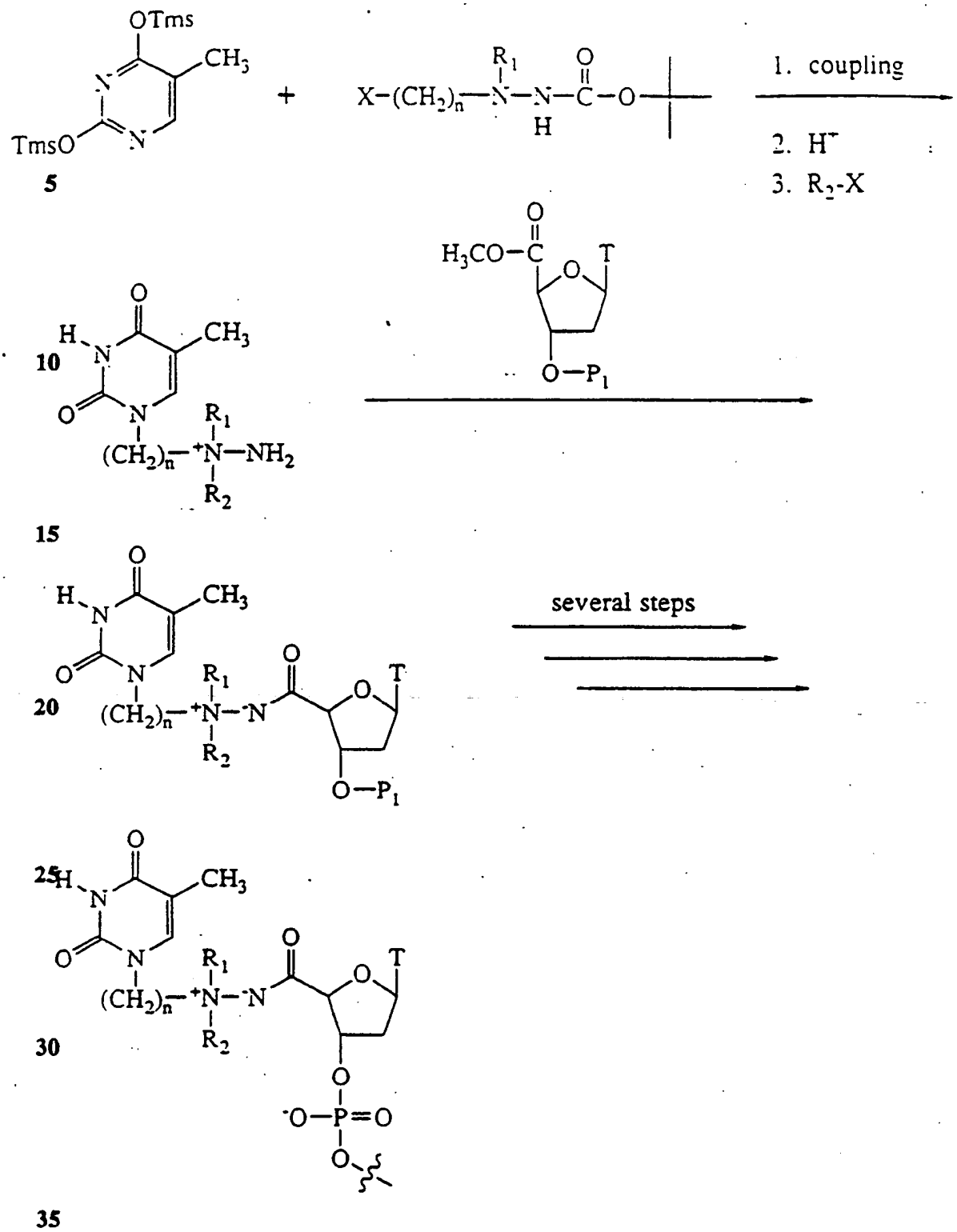
The art of nucleotide and oligonucleotide synthesis has provided a great variety of suitably blocked and activated furanoses and other intermediates which are expected to be very useful in the construction of aminimide-based mimetics. (Comprehensive Organic Chemistry, Sir Derek Barton, Chairman of Editorial Board, Vol. 5, E. Haslam, Editor, pp. 23-176).

A great variety of nucleotide and oligonucleotide structural motifs incorporating aminimide-based structures are contemplated including, but not limited to, the following.

(1) For the synthesis of oligonucleotides containing peptidic aminimide-based linkers in place of the phosphate diester groupings found in native oligonucleotides, the following approach is one of many that can be used.



(2) For the synthesis of structures in which an aminimide grouping is used to link complex oligonucleotide-derived units, an approach such as the following can be very useful.



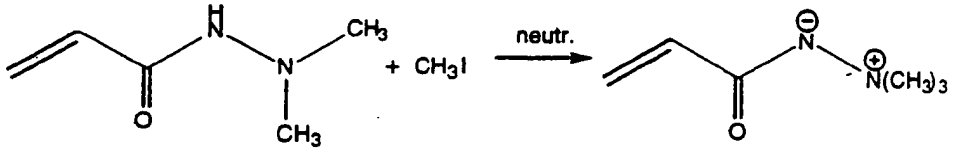
EXAMPLES

In order to exemplify the results achieved using the aminimides of the present invention, the following examples are provided without any intent to limit the scope of the instant invention to the discussion therein, all parts and percentages are by weight unless otherwise indicated.

EXAMPLE 1

Synthesis of a vinyl aminimide monomer

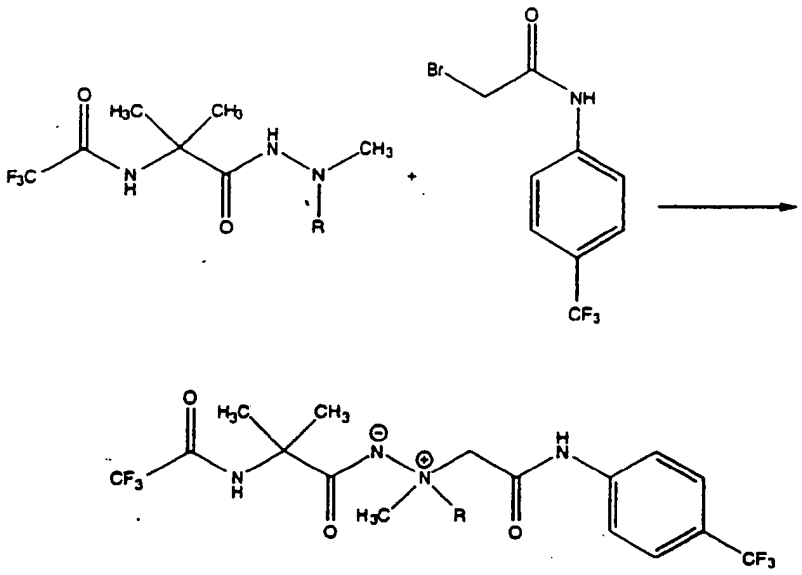
This example illustrates the alkylation of 1,1-dimethyl-2-acryloylhydrazide by treatment with an equimolar amount of methyl iodide in acetonitrile.



This reaction is carried out with equimolar quantities of the reactants dissolved in acetonitrile (0.1 mol ea/100 mL) under gentle reflux overnight. The mixture is concentrated on a rotary evaporator, methanol is added and the pH is adjusted to the phenolphthalein end point with methanolic KOH. The solvents are removed *in vacuo*, the residue is dissolved in the minimum amount of benzene, the precipitated salts are removed by filtration and the crude product is isolated by removal of solvents to dryness. Purified monomer is obtained by recrystallization from ethyl acetate.

EXAMPLE 2

Synthesis of a trifluoroacyl dipeptide analide elastase inhibitor peptidomimetic:

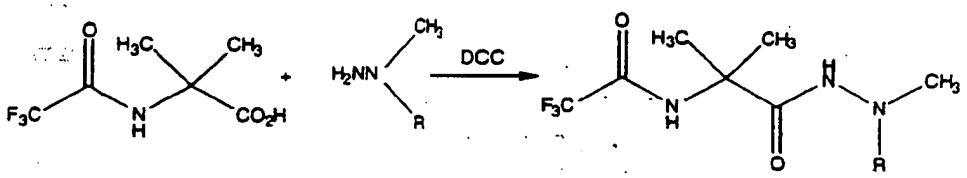


An equimolar mixture of an a-halo carbonyl compound (such as 2-bromoacetyl-4'-isopropylanilide) ana dialkylhydrazide (such as *N*-(2-trifluoroacetamidoisobutyryl)-*N'*-benzyl-methylhydrazine) in acetonitrile; at a final concentration of ca. 0.1M is heated at reflux for periods ranging from 1-6 days, depending on the solvent employed, with the progress of the reaction being monitored by in-process TLCs. On completion of the reaction the mixture is cooled and the solvent removed in vacuo. In the case of the aqueous reaction conditions the mixture is partitioned between water and a suitable organic solvent to dissolve the aminamide (e. g. chloroform). The solvent is removed in vacuo and the residue is recrystallized from a solvent such as ethyl acetate to afford crystals of the aminamide. In reactions which did not employ water as a cosolvent, the residue is treated with one equivalent of 1.0M KOH in MeOH and gently warmed for 10-15 minutes to ensure complete formation of the ylide. The methanol is

removed in vacuo and the residue triturated with THF and filtered to remove the KBr formed. The residue is recrystallized as for the aqueous case above from a solvent such as ethyl acetate to afford crystals of the aminamide. The yields of the aminamide from the aqueous solvent systems are superior, providing cleaner crude reaction mixtures and superior yields. Using this method *N*-isobutyl-*N*-methyl-*N*-(2-acetyl-(4'-isopropylanilide))-amin-*N*'-(2-trifluoroacetamidoisobutyramide, *N*-benzyl-*N*-methyl-*N*-(2-acetyl-(4'-trifluoromethylanilide))-amin-*N*'-(2-trifluoroacetamidoisobutyramide, and *N*,*N*-dimethyl-*N*-(2-acetyl-(4'-trifluoromethylanilide))-amin-*N*'-(2-trifluoroacetamido isobutyramide are synthesized. These mimetic ligands are useful as inhibitors of human leucocyte elastase and porcine pancreatic elastase.

EXAMPLE 3

Synthesis of trifluoromethyl hydrazide modules:.



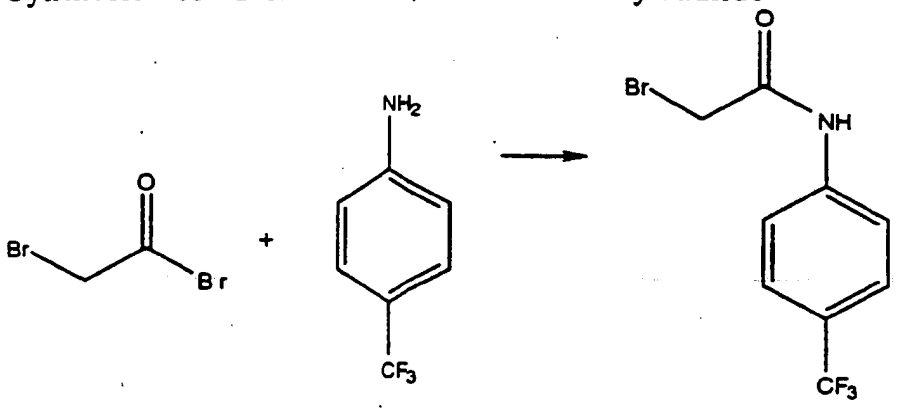
N-(2-trifluoroacetamidoisobutyryl)-*N*'-isobutyl-methylhydrazine (TFA-AIB isobutylmethylhydrazide) - A solution of 2-trifluoroacetamidoisobutyric acid (796 mg, 4.0 mmol) in dry THF (15 ml) is stirred while dicyclohexyl-carbodiimide (824 mg, 4.0 mmol) is added. The reaction is subsequently strirred for three minutes, after which 1-isobutyl-1-methylhydrazine (408 mg, 4.0 mmol) is added neat. Dicyclohexylurea precipitated immediately. The resultant suspension is stirred for one hour, filtered to remove the insoluble urea and the solvent is removed on a rotary evaporator to afford an off white solid (1.11 g, 98%) which

exhibited spectral properties consistent with those expected for *N*-(2-trifluoroacetamidoisobutyryl)-*N'*-isobutyl-*N'*-methyl-hydrazine.

In a similar manner, *N*-(2-trifluoroacetamidoisobutyryl)-*N'*-benzyl-methylhydrazine, *N*-(2-trifluoroacetamidoisobutyryl)-*N',N'*-dimethylhydrazine, and *N*-(2-trifluoroacetamidoisobutyryl)-*N',N'*-pentamethylene-hydrazine are prepared in comparable yields from 2-trifluoroacetamido-isobutyric acid and the respective 1,1-dialkylhydrazines.

EXAMPLE 4

Synthesis of 2-bromacet-4,-trifluoromethylanalide



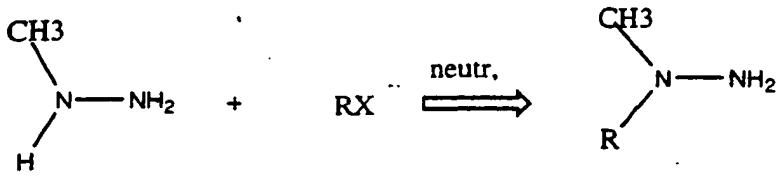
To a biphasic mixture consisting of diethyl ether (300 ml), 4-trifluoromethylaniline (aminobenzotrifluoride, 25.0g, 0.155 mole) and aqueous NaOH (1M, 200 ml) cooled to 0 ^{0}C is added, with vigorous stirring, a solution of bromoacetyl bromide (37.6 g, 16.2 ml, 0.186 mole) in diethyl ether (150 ml) over one hour. The reaction is stirred an additional ten minutes at 0^{0}C and the layers are then separated. The aqueous phase is extracted with ether (200 ml) and the combined organic layer are dried (sat'd aq NaCl, Na_2SO_4) and concentrated to afford 47 g of a yellow oil. Crystallization from ethyl acetate afforded two crops of pale yellow rod-like crystals (27.9, then 11.3 g, 89%) which exhibited spectral

properties consistent with those expected for 2-bromoacet-4'-trifluoromethylanilide.

In the same fashion 2-bromoacet-4'-isopropylanalide was made (74.9g, 79%) and characterized

EXAMPLE 5.

Synthesis of 1-substituted-1-methyl hydrazine modules



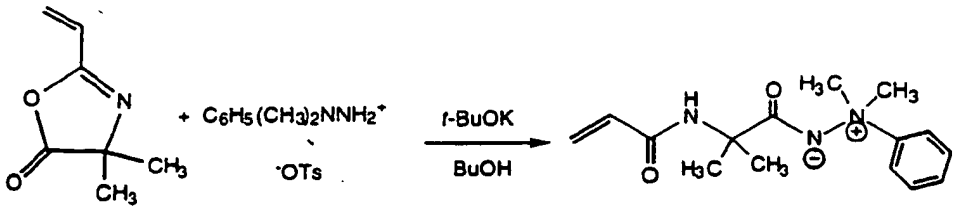
1-benzyl-1-methylhydrazine - A solution of methylhydrazine (46 g, 1 mole) in THF (200 ml) is cooled at 0^0C and a solution of benzyl bromide (57.01g, 0.3 mole) in THF (100 ml) is added dropwise with stirring over a period of 30 minutes. The reaction is stirred at 0 ∞C for another 15 minutes, then heated to reflux and held at reflux for two hours. A water-cooled downward condenser is set up and approximately half of the solvent is removed by distillation. The residue is poured into water (200 ml), which is then made basic by the addition of concentrated aqueous NaOH. The layers are separated, the aqueous phase (ca. 250 ml) is extracted with ether (2 x 200 ml) and the combined organic phases are washed (1 x 100 ml H_2O), dried (sat'd aq NaCl, $MgSO_4$) and concentrated by distillation to give 54 g of a yellow oil. Distillation at reduced pressure afforded 1-benzyl-1-methylhydrazine as a colorless liquid (b. p. 103-107, 16 mm Hg, 19.8 g, 48%), which exhibited spectral properties consistent with those reported previously.

In a similar manner, 1-isopropyl-1-methylhydrazine 12.3g, 42%); 1-(*tert*-butyl 2-acetyl)-1-methylhydrazine (3.40g, 42%); 1-isobutyl-1-methylhydrazine (9.80g, 29%), and 1-(2-(3-indolyl)-ethyl)-1-methylhydrazine

(1.32g, 69%) are prepared from the respective alkyl bromides and characterized.

EXAMPLE 6

Synthesis of a vinyl oxazolone-derived aminimide monomer:

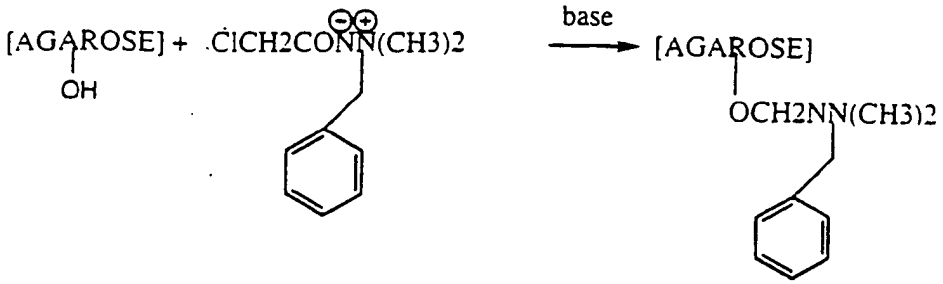


This reaction is carried out by stirring equimolar amounts of the 1,1,1-trialkylhydrazinium tosylate (prepared from 1-methyl-1-phenyl hydrazine and *p*-toluenesulfonic acid in toluene) in *t*-butanol at room temperature overnight. An equimolar amount of 2-vinyl-4,4-dimethylazlactone (SNPE Chemical Inc.) is added and, the solution is stirred an additional 6 hours. An equal volume of toluene is added. The system is filtered and the filtrate is concentrated *in vacuo* on a rotary evaporator to yield the product as a thick oil. Pure crystalline product is obtained by crystallization from acetone.

EXAMPLE 7

Preparation of aminimide-functionalized agarose:

This example is illustrated for functionizing commercially available 6% crosslinked agarose with 1-benzyl-1,1-dimethyl chloromethyl aminimide (prepared from 1-benzyl-1,1-dimethylhydrazinium chloride [from 1,1-dimethylhydrazine and benzyl chloride in toluene] to produce the aminimide functionalized agarose, useful as a hydrophobic interaction support material for the chromatographic separation of proteins .



This reaction is carried out by steeping the agarose with potassium *t*-butoxide in a mixture of *t*-butanol and DMF under nitrogen for one hour at room temperature. The hydrazinium salt is added, and the mixture is stirred for 24 hours. The functionalized agarose is collected by filtration, washed with *t*-butanol, methanol and finally with water. This material is stored in water for future use.

EXAMPLE 8.

Construction of a trimeric species using an epoxidation iteration: An example of stepwise polymerization with MW ± 1 Dalton.

A mixture of styrene oxide (12.02 g, 0.1 mole), 1,1-dimethylhydrazine (6.01 g, 0.1 mole), and methyl 4-pentenoate (11.41 g, 0.1 mole) in methanol (150 mL) is stirred at room temperature for four days. The solvent is removed *in vacuo* to afford a white solid (26.4 g, 101%, >95% pure).

This solid is dissolved in methylene chloride (300 mL) and cooled to 0 °C while a solution of *m*-CPBA (51.8 g, 50-60%, ca. 0.15 mole) in methylene chloride (200 mL) is added. The mixture is stirred until the alkene is consumed (this reaction is followed by ^{1}H-NMR). The mixture is extracted with 1.0 M NaOH solution (500 mL) and the organic layer is dried (saturated NaCl, anhydrous Na_2SO_4) and concentrated to afford a cream-colored solid (29.3g, 106%) which is recrystallized from methanol to afford the epoxy aminimide (26.3g, 95%).

This epoxide (0.095 mole) is treated with 1,1-dimethylhydrazine (5.73 g, 0.095 mole) in methanol (100 mL

and is refluxed for eight hours. The mixture is cooled and methyl 4-pentenoate (10.87 g, 0.095 mole) in methanol (100 mL) is added. The resultant solution is stirred at room temperature for 48 h. The solvent is removed to provide a pale yellow solid (45.6 g, 114%). Treatment of this material with *m*-CPBA (ca. 1.5 eq) in methylene chloride provides, after recrystallization, colorless crystals of the epoxydiaminimide (38.2 g, 0.091 mole, 96%).

The epoxide is treated with 1,1-dimethylhydrazine (5.47 g, 0.091 mole) in methanol (100 mL) at room temperature and the ylide which is formed *in situ* is acylated by the addition of methyl 4-pentenoate (10.39 g, 0.091 mole). Treatment of the crude reaction mixture with excess *m*-CPBA in methylene chloride affords the epoxide (47.64 g, 0.08 mole).

Purification and iteration of the previous steps can provide a polymer which has an exact molecular weight of 120 + N(158) Da where N is the number of condensing steps.

EXAMPLE 9.

Construction of a functionalized surface via hydrazine ester condensation with epoxy silica.

A slurry of epoxy silica (10.0 g, 15 m Exsil C-200 silica, *vide infra*) in methanol (100 mL) is treated with 1,1-dimethylhydrazine (6.01 g, 0.1 mole), and stirred at room temperature for two hours (mechanical stirring provides a more efficient preparative procedure, as well as a superior product). To this slurry is added methyl 4-pentenoate (11.41 g, 0.1 mole) and the resultant mixture is mechanically stirred for five days. The functionalized silica is collected by filtration and washed by repeatedly suspending in methanol and filtering to removed the soluble material. After six washings, the solid obtained is dried overnight in a vacuum oven (60 °C/0.1 mm Hg) to afford 9.86 g of product.

This material is suspended in methylene chloride and treated with *m*-CPBA (51.8 g, 50-60%, ca. 0.15 mole). The suspension is stirred mechanically overnight at room

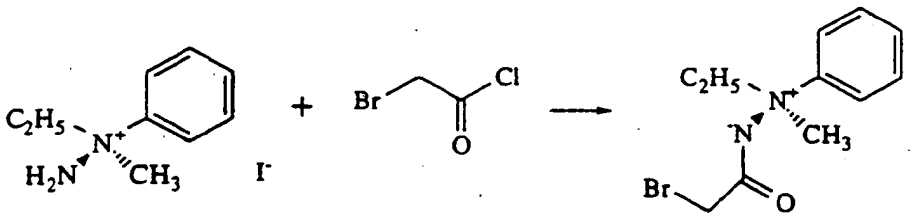
temperature and washed with methanol, as before, to remove the unreacted and spent reagents. The solid is dried overnight in a vacuum oven (60 °C/0.1 mm Hg) to afford 9.83 g of product.

This homologous epoxy silica is slurried in methanol (100 mL) and treated with 1,1-dimethylhydrazine (6.01 g, 0.1 mole). The suspension is stirred at room temperature for two hours and methyl 4-pentenoate (11.41 g, 0.1 mole) is added. After five days, the material is collected by filtration and washed repeatedly with methanol as above. Drying this material overnight in a vacuum oven (60 °C/0.1 mm Hg) affords 9.88g of the alkene-functionalized surface.

Further iteration of the epoxidation and hydrazine-ester condensations provides silica beads with known functionality (or functionalities) and size (or sizes).

EXAMPLE 10.

Acylation of *S*-1-ethyl-1-methyl-1-phenylhydrazinium iodide with bromoacetyl chloride:

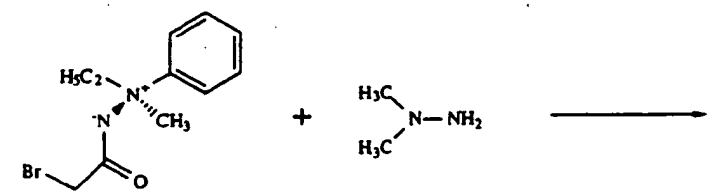


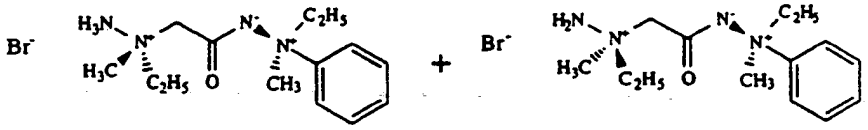
A solution of *S*-1-ethyl-1-methyl-1-phenylhydrazinium iodide (2.78 g, 10 mmol) in benzene (50 mL) and pyridine (2.38 g, 30 mmol, 2.42 mL) is cooled to 0 °C, then treated with a solution of bromoacetyl chloride (1.73 g, 11 mmol, 0.91 mL) in benzene (10 mL). The mixture is stirred at 0 °C for one hour, then room temperature for two hours. During the course of the reaction, the pyridinium salts precipitate and subsequently are removed by filtration.

Following removal of the solvent, the residue is recrystallized from ethyl acetate to afford pale yellow crystals of 2-bromoacetyl-*S*-1-ethyl-1-methyl-1-phenylhydrazinium inner salt (2.24 g, 78%). Alternatively, Amberlite IR-45 resin can be used in place of pyridine to extract the acidic protons. The resin is conveniently removed by filtration.

EXAMPLE 11.

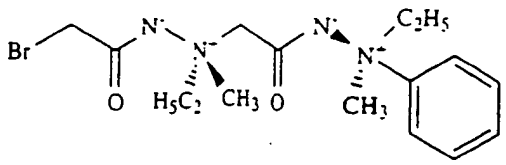
Homologation of 2-bromoacetyl-*S*-1-ethyl-1-methyl-1-phenylhydrazinium inner salt by alkylation of an hydrazine followed by acylation.





A mixture of 2-bromoacetyl-*S*-1-ethyl-1-methyl-1-phenylhydrazinium inner salt (2.24 g, 7.8 mmol) in THF (100 mL) is cooled to 0 °C while a solution of 1-ethyl-1-methyl-hydrazine (6.96 g, 0.94 mmol) in THF (25 mL) is added dropwise. The mixture is stirred for 15 minutes at 0 °C, then room temperature overnight. The resultant suspension is filtered. The precipitated diastereomers are isolated as a white powder (2.36 g, 84%).

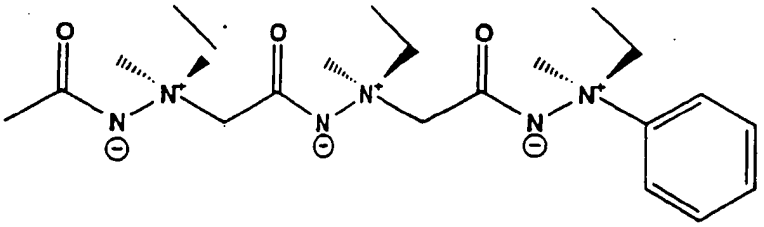
The diastereomers from the above reaction are separated on a C-18 reverse phase silica media with an acetonitrile-water gradient. The fractions containing the desired diastereomer are pooled, and the product is isolated by removal of the solvents *in vacuo*.



The resulting dried powder from the above reaction is dissolved in benzene and pyridine (1.59 g, 20 mmol, 1.61 mL or Amberlite IR-45 resin, *vide supra*), then cooled to 0 °C while a solution of bromoacetyl chloride (1.13 g, 7.2 mmol, 0.59 mL) in benzene (10 mL) is added. The mixture is stirred overnight at room temperature. The pyridinium salts are subsequently removed by filtration and the filtrate is concentrated to afford a pale yellow solid (1.87 g). The pure material is obtained by recrystallization of the yellow solid from ethyl acetate.

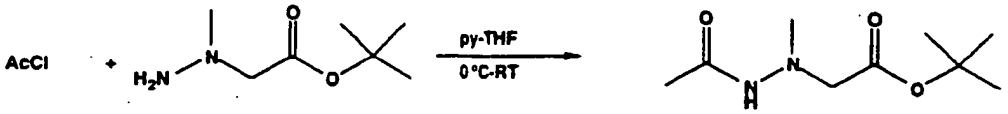
The material from the above reaction is dissolved in THF (50 mL), then treated with 1-ethyl-1-methylhydrazine (0.46 g, 6.2 mmol) in THF (10 mL) at 0 °C. The mixture is stirred overnight at room temperature. The volume of the reaction mixture is reduced by approximately half, then the precipitate is filtered and washed with cold ether to afford a white powder (1.36 g, 72%). The diastereomers are again separated on a C-18 reverse phase silica media with an acetonitrile-water gradient. The fractions containing the desired diastereomer are pooled and the product is isolated by removal of the solvents *in vacuo*.

The product from the above step is dissolved in benzene (20 mL) and pyridine (0.71 g, 9 mmol, 0.73 mL or Amberlite IR-45 resin, *vide supra*), then cooled to 0 °C while a solution of acetyl chloride (0.35 g, 4.4 mmol, 0.31 mL) in benzene (5 mL) is added. The resultant mixture is stirred overnight at room temperature. The mixture is filtered and the solvent is removed *in vacuo* to afford an orange gum (2.13 g). Crystallization of this material from ethyl acetate gave the trimeric aminimide stereoisomer shown below:

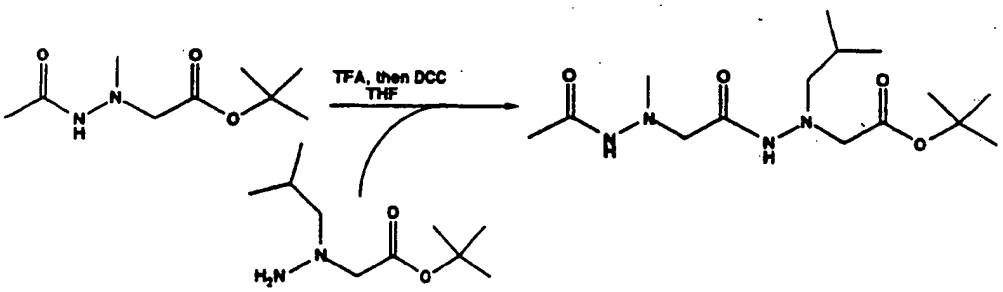


EXAMPLE 12.

Synthesis of an hydrazinium backbone via hydrazide homologation.

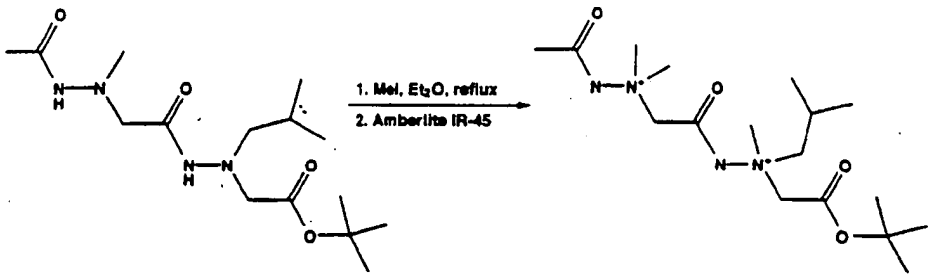


Acetyl chloride (8.64 g, 0.11 mole) is added to an ice-cooled solution of *N*-amino-*N*-methylglycine *tert*-butyl ester (11.6 g, 0.10 mole) in pyridine (10 mL) and THF (250 mL). The mixture is stirred at 0 °C for 30 minutes, then room temperature for three hours. The mixture is concentrated on a rotary evaporator and the remaining volatiles are removed *in vacuo*. The residue is recrystallized from ether to afford the hydrazide ester (14.54 g, 0.092 mole).



The product is dissolved in THF (300 mL) and treated with trifluoroacetic acid (0.1 mL, 148 mg, 1.3 mmoles). This mixture is stirred at room temperature for two hours, then a solution of *N,N'*-dicyclohexylcarbodiimide (19.22 g, 0.093 mole) in THF (100 mL) is added followed by the addition of a

solution of *N*-amino-*N*-(2-methylpropyl)-glycine *tert*-butyl ester (14.74 g, 0.094 mole) in THF (100 mL). The precipitate (dicyclohexylurea) is removed by filtration and the filtrate is concentrated on a rotary evaporator to afford an amorphous mass, which yields white crystals (27.06 g, 89%, 0.082 mole) after recrystallization from ethyl acetate.



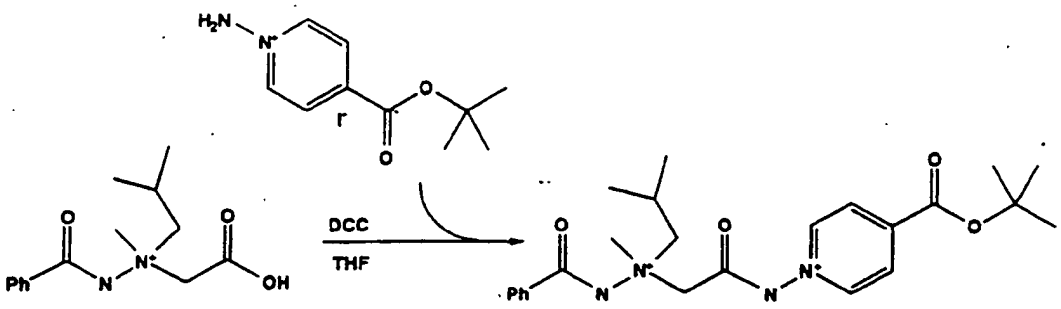
A solution of this bis-hydrazide (27.06 g, 0.082 mole) in diethyl ether (300 mL) is treated with methyl iodide (17.3 g, 0.12 mole) and refluxed for twelve hours. The reaction mixture is concentrated to remove excess methyl iodide, and dissolved in isopropanol (200 mL). Amberlite IR-45 resin is added and the solution is stirred at room temperature for eight hours. The solids are removed by filtration and the solvent is reduced to saturation. This saturated solution is cooled to -20 °C for 36 hours, and the resultant crystals are collected by filtration to afford bis-hydrazinium inner salt (21.42 g, then 5.87 g, 93%) as a racemate.

EXAMPLE 13.

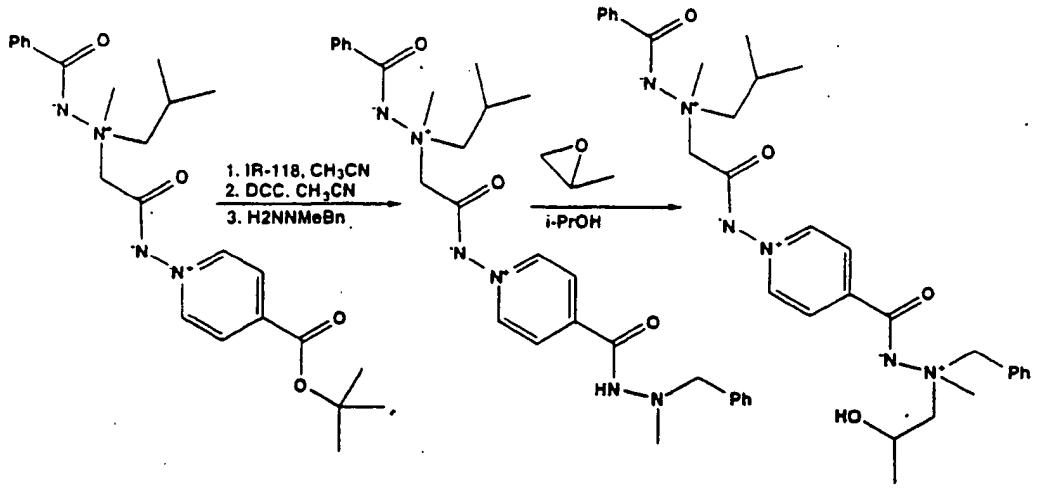
Incorporation of an aminopyridinium functionality into an aminimide backbone.

A solution of 1-amino-4-pyridiniumcarboxylic *tert*-butyl ester iodide (3.22 g, 10 mmol) in THF (25 mL) is added to a solution of *N*-benzoyl-*N'*-acetate-*N'*-isobutyl-*N'*-methylhydrazinium inner salt (2.64 g, 10 mmol) and *N,N'*-dicyclohexylcarbodiimide (2.06 g, 10 mmol) in THF (100 mL) and stirred for two hours at room temperature. The

suspension is treated with Amberlite IR-45 (or an equivalent basic resin) for three hours at room temperature, then filtered to remove both the resin and precipitated dicyclohexylurea. The filtrate is concentrated, and the residue is recrystallized from ethyl acetate to afford the bis hydrazinium inner salt (3.56 g, 78%).



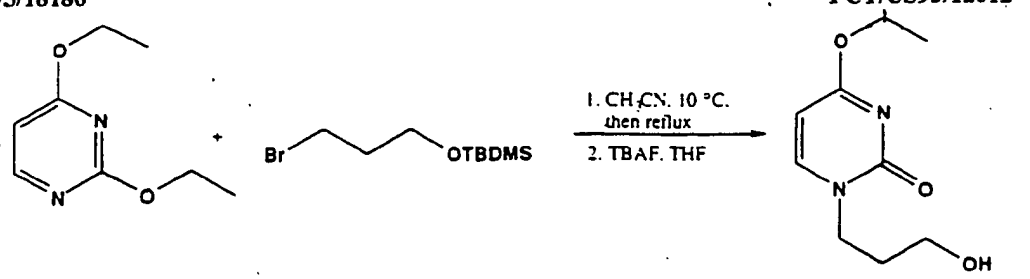
The entirety of this material is dissolved in acetonitrile (150 mL), and Amberlite IR-118 is added. The mixture is refluxed until the ester is completely consumed. The resin is removed by filtration and the solution is treated with *N,N'*-dicyclohexylcarbodiimide (1.61 g, 7.8 mmol) in acetonitrile (25 mL). After three minutes of stirring, 1-benzyl-1-methylhydrazine (1.38 g, 9.36 mmol) is added neat, and the resultant suspension is stirred at room temperature for two hours. Removal of the precipitated dicyclohexylurea by filtration, and concentration of the filtrate, affords a solid (5.01 g), which is dissolved in isopropyl alcohol (100 mL). Propylene oxide (0.542 g, 9.36 mmol) is added. The mixture is refluxed for seven hours, then the volatile components are removed *in vacuo*. Crystallization of the residue from ethyl acetate provides the tris-ylide (2.95 g, 5.30 mmol, 68 %).



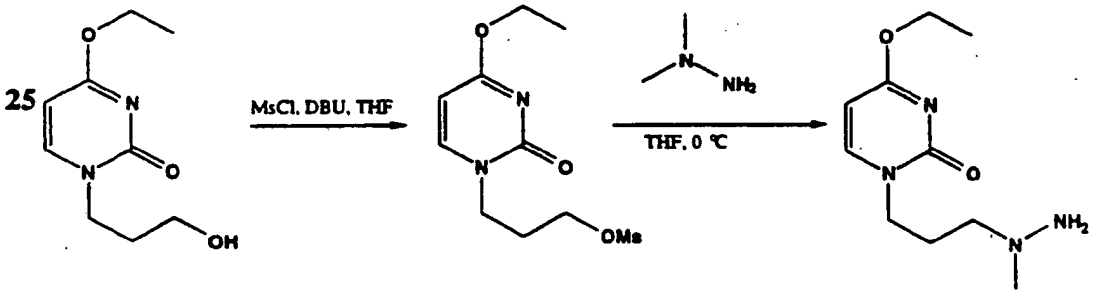
EXAMPLE 14.

Synthesis of an hydrazine tethered pyrimidinone via quaternization.

A mixture of 2,4-diethoxypyrimidine (16.8 g; 0.1 mole) in acetonitrile (250 mL) is cooled in an ice bath while a solution of 3-bromo-1-*tert*-butyldimethylsilyloxypropane (25.3 g, 0.1 mole) in acetonitrile (150 mL) is added. The rate of addition is adjusted so that the internal reaction temperature does not exceed 10 °C. The mixture is stirred at 0 °C for two hours, then refluxed for 10 h. The solvent is removed *in vacuo*. The residue is dissolved in THF (200 mL), and a solution of tetra-*n*-butylammonium fluoride in THF is added (1.0 M, 100 mL). The orange solution is stirred at room temperature for one hour, then is poured into brine (300 mL). The layers are separated and the aqueous phase is extracted with ether (2 x 200 mL). The combined organic extracts are dried over sodium sulfate, filtered and concentrated to afford an orange oil (36.7 g). This oil is chromatographed on silica gel (gradient elution with EtOAc-Hexanes) to provide the pure alcohol (13.1 g, 0.066 mole, 66%).



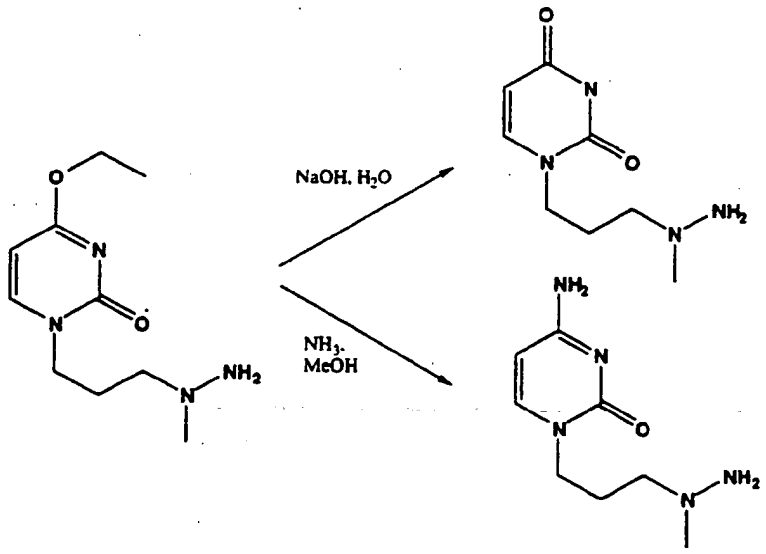
This alcohol is dissolved in THF (200 mL), and treated with methanesulfonyl chloride (9.07 g, 0.079 mole, 6.12) and 1,8-diazabicyclo[5.4.0]undec-7-ene (12.05 g, 0.079 mole, 11.84 mL) at 0 °C for two hours. The mixture is transferred via cannula into an ice-cooled solution of methylhydrazine (15.2 g, 0.33 mole, 17.6 mL) in THF (100 mL). The reaction is stirred at 0 °C for four hours, then room temperature for two hours. This mixture is poured into 200 mL of a solution of 1 M Na_2CO_3 saturated with NaCl. The layers are separated, and the aqueous phase is extracted with diethyl ether (2 x 200 mL). The combined organics are dried over sodium sulfate and concentrated to afford an amber syrup. Column chromatography on silica gel (gradient elution with chloroform-methanol) provided the pyrimidylhydrazine in 48% yield (6.77g).



A solution of this hydrazine (2.14 g, 10 mmol) in 1.0 M NaOH (30 mL) is warmed gently to exhaustion of the starting material. The reaction mixture is lyophilized, and the resulting powder is triturated with THF to dissolve the hydrazine. Filtration of the salts and concentration of the

filtrate affords nearly pure 1-(3-(1-uridyl)-propyl)-1-methylhydrazine (1.80 g, 97%).

In another flask, the pyrimidyl hydrazine (2.14 g, 10 mmol) is treated with an excess of anhydrous ammonia in methanol at 0 °C, then stirred at room temperature overnight. Removal of the solvent on a rotary evaporator afforded a residue which was chromatographed on silica gel (gradient elution with chloroform-methanol), providing the pure 1-(3-(1-cytidyl)-propyl)-1-methylhydrazine (1.62 g, 87%).

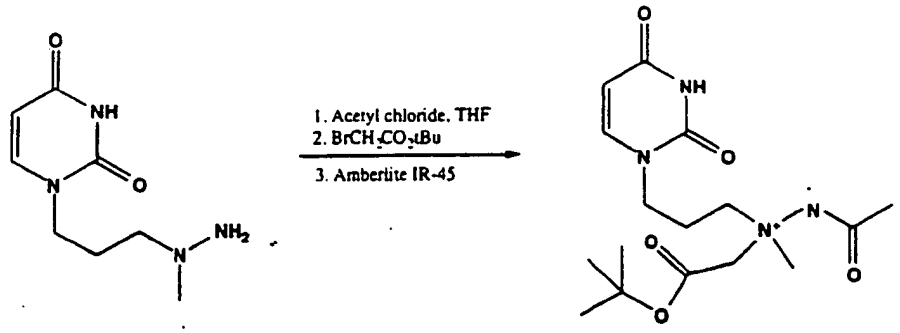


EXAMPLE 15.

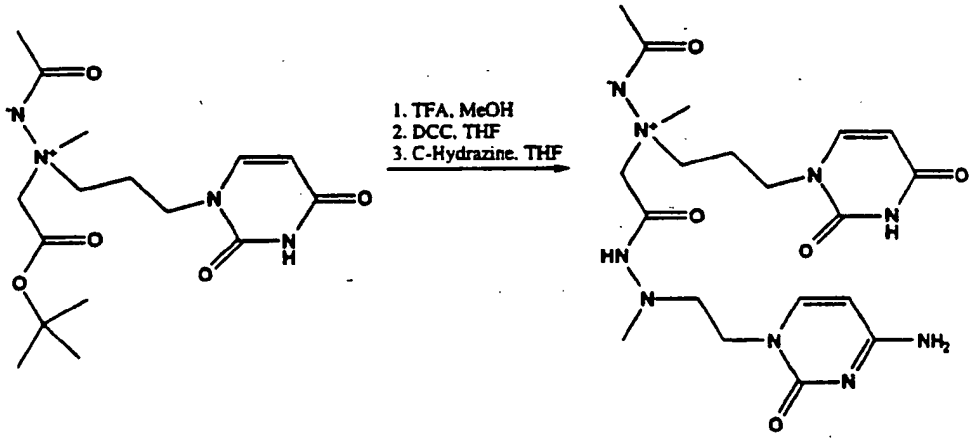
Stepwise assemblage of a modular scaffold which presents a known sequence of nucleotides to a desired target.

A solution of 1-(3-(1-uridyl)-propyl)-1-methylhydrazine (186 mg, 1.0 mmol) in THF (10 mL) is treated with acetyl chloride (79 mg, 1.0 mmol, 72 mL). The resultant solution is stirred at room temperature for three hours. This mixture is transferred via cannula into an ice-cooled solution of *tert*-butyl bromoacetate (195 mg, 1.0 mmol, 161 mL) in THF (5 mL). The hydrazinium bromide is converted to the inner salt by treatment of the suspension with Amberlite IR-45 resin. The volatile components are remove *in vacuo*, and the residue

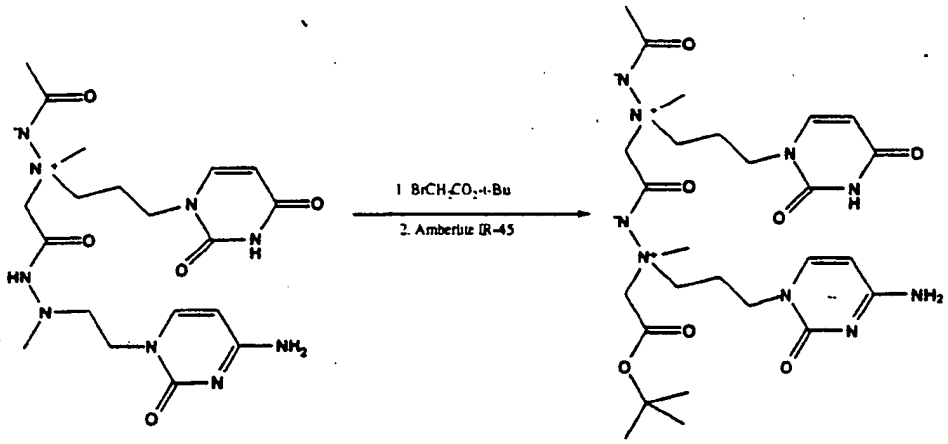
is recrystallized from ethyl acetate to afford the 2-acetyl-1-(3-(1-uridyl)-propyl)-1-(*tert*-butyl 2-aceto)-1-methylhydrazinium inner salt (265 mg, 75%).



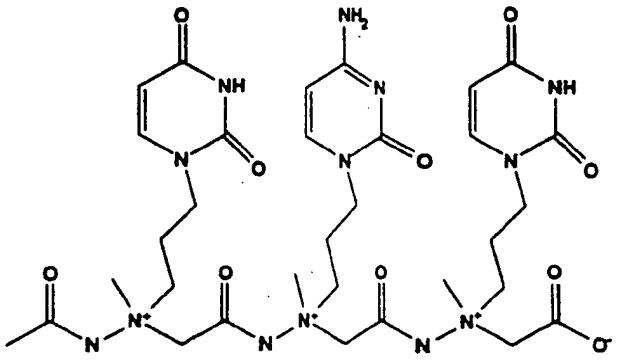
This material was dissolved in methanol (10 mL) and three drops of trifluoroacetic acid are added. After 10 minutes at room temperature, the mixture is concentrated on a rotary evaporator. To a solution of this crude acid in THF (10 mL) is added *N,N'*-dicyclohexylcarbodiimide (155 mg, 0.75 mmol). The resultant mixture is treated with 1-(3-(1-cytidyl)-propyl)-1-methylhydrazine (140 mg, 0.75 mmol) in THF (10 mL). The white suspension is stirred for two hours, filtered to remove the precipitated urea, and the filtrate concentrated. The residue is recrystallized from methanol to afford the hydrazide (220 mg, 0.48 mmol, 65%).



This material is treated with *tert*-butyl bromoacetate (94 mg, 0.48 mmol, 77 mL) in THF (5 mL). The hydrazinium bromide is converted to the inner salt by treatment of the suspension with Amberlite IR-45 resin. The volatile components are remove *in vacuo*, and the residue is purified by column chromatography on RP C-18 silica (gradient elution with MeOH-Water) to afford the bis-hydrazinium inner salt (208 mg, 0.38 mmoles).



Deprotection and reiteration of the above steps with the uridyl substituted hydrazine provides the tris-hydrazinium inner salt, which presents the sequence U-C-U as a recognition sequence for the RNA codon A-G-A.

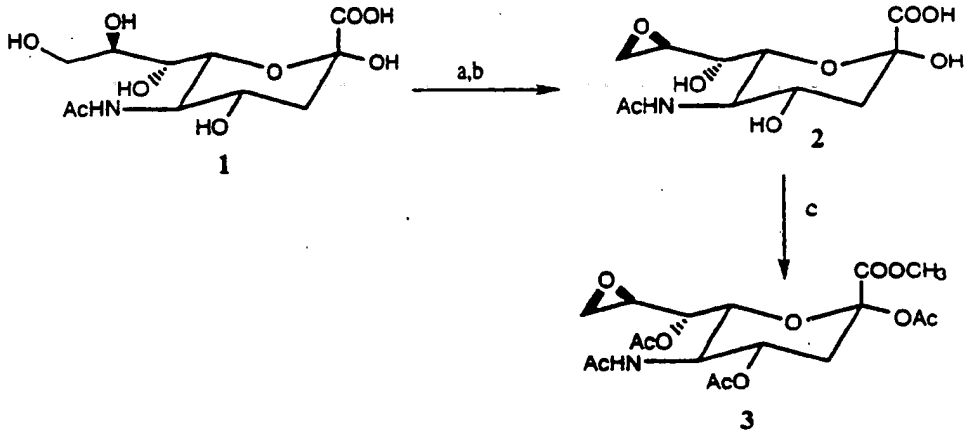


As can be seen, this series of reaction can be repeated, substituting the five natural bases as well as other bases for each step as the desired sequence dictates or warrants. This material also can be elongated using silyl protected purines, which prevents inter- and intramolecular binding of the bases. In some cases, the ring amine of the cytidyl hydrazine is protected as well, by a trialkylsilyl group prior to incorporation into the backbone.

EXAMPLE 16.

Synthesis of carbohydrate modules for incorporation into aminimide backbone scaffolds

Module I



(a) p-TsCl (1 eq), Pyridine, rt
(b) DBU, diethyl ether, rt
(c) Ac_2O, Pyridine, CH_2Cl_2, rt

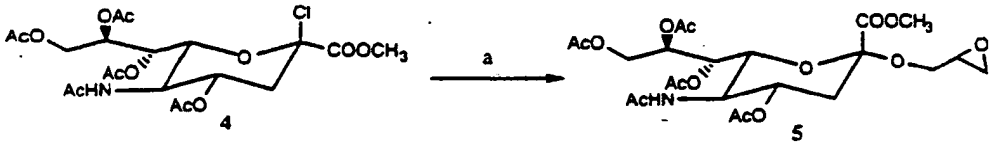
To a solution of sialic acid (1 g, 3.23 mmol) in pyridine (2.9 mL, 37 mmol, 11 equiv) is added *p*-Toluenesulfonyl chloride (620 mg, 3.23 mmol, 1.0 equiv). The reaction mixture is stirred at room temperature for 12 h. The

crude mixture is quenched with water, then extract with diethyl ether several times. The combined organic extract is washed with 1 N HCl, dried with $MgSO_4$, filtered and concentrated on a rotary evaporator to give the crude product (1.4 g, 95%).

To the tosylate from the above reaction (1 g, 2.16 mmol) in a suitable solvent, such as diethyl ether (10 mL), is added DBU (821 mg, 5.4 mmol, 2.5 equiv). The mixture is stirred at room temperature for 5 h. The crude mixture is washed with 1 N HCl, then saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated to obtain epoxide **2** (566 mg, 90%).

To a solution of epoxide **2** (500 mg, 1.7 mmol) in pyridine (695 mL, 8.6 mmol, 10 equiv) is added acetic anhydride (1.05 g, 10.3 mmol, 6 equiv). The reaction mixture is heated on a steam bath for 6 h. The excess pyridine, acetic anhydride and the acetic acid are removed at reduced pressure. The resulting residue is purified by column chromatography to obtain pure **3** (683 mg, 92%).

Module II

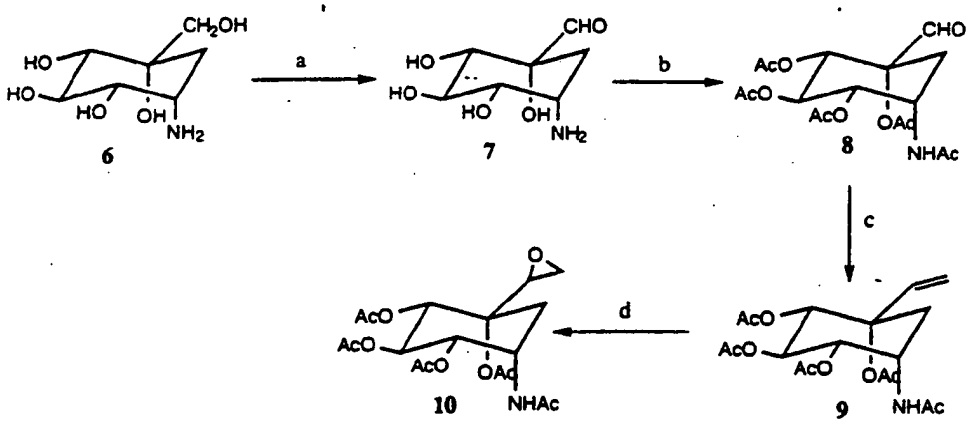


(a) Glycidol, Ag-Salicylate, C_6H_6, rt

To a solution of **4** (500 mg, 0.98 mmol), in a suitable solvent such as benzene (6 mL), is added Ag-Salicylate (265 mg, 1.08 mmol, 1.1 equiv). After 10 min at room temperature, glycidol (73 mg, 0.98 mmol, 1.0 equiv) is added to the mixture. The reaction mixture is stirred at room

temperature for 2 h. Water is added to quench the reaction. The organic solution is then washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. Purification with column chromatography gives **5** (483 mg; 90%).

Module III



(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C
(b) Ac_2O, Pyridine, CH_2Cl_2, rt
(c) Ph_3PCH_2I, PhLi, THF, rt
(d) m-CPBA, CH_2Cl_2, rt

A three neck round-bottom flask is charged with 10 mL of a suitable solvent, such as CH_2Cl_2, and oxalyl chloride (540 mL, 6.2 mmol, 1.2 equiv). The solution is stirred and cooled to -60 °C as DMSO (740 µL, 810 mg, 10.4 mmol, 2 equiv) in dichloromethane (5 mL) is added dropwise at a rapid rate. After 5 min, **6** (1 g, 51.8 mmol, 1.0 equiv) is added dropwise over 10 min period, maintaining the temperature at -60 °C. After an additional 15 min, triethylamine (7.2 mL, 51.8 mmol, 10 equiv) is added dropwise, keeping the temperature at -60 °C. Stirring is continued for 5 min. The mixture is warmed to room temperature, and water is added. The aqueous layer is separated and extracted with a polar solvent, such as ethyl

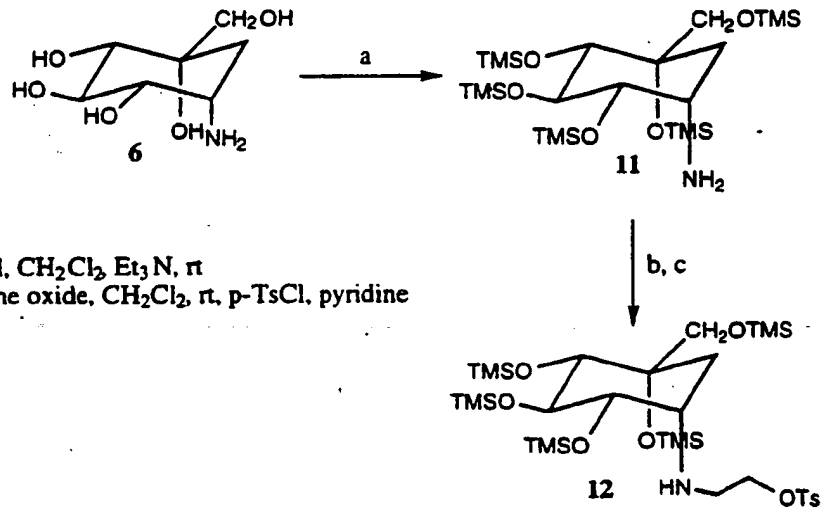
acetate. The organic layers are combined, washed with 1% HCl until acidic, then washed again with saturated sodium chloride and dried over anhydrous magnesium sulfate. The filtered solution is concentrated by rotary evaporation to obtain the aldehyde 7 (890 mg, 90%).

To a solution of 7 (800 mg, 4.2 mmol) in pyridine (3.4 mL, 42 mmol, 10 equiv) is added acetic anhydride (3 g, 29.3 mmol, 7 equiv). The reaction is stirred at room temperature for 12 h. The excess pyridine, acetic anhydride and acetic acid are removed at reduced pressure. The residue is purified by column chromatography to give **8** (1.48 g, 88%).

A 50 mL, three-neck, round bottom flask, equipped with a pressure-equalizing dropping funnel, thermometer, magnetic stirring bar, and serum caps, is charged with methyltriphenylphosphonium iodide (1.1g, 2.74 mmol, 1.1 equiv) and THF (10 mL), then flushed with argon. The flask is cooled in an ice bath, and the suspension is stirred under a positive pressure of argon while 5 µL to 14 µL of 1.8 M phenyllithium in 30:70 ether:cyclohexane is added dropwise until the suspension develops a permanent yellow color. 1.6 mL of 1.8 M phenyllithium is added dropwise over 10 min. The ice bath is removed, and the orange suspension containing excess phosphonium salt is stirred at room temperature for 30 min. The reaction mixture is stirred and cooled to 0-5 °C. Compound **8** (1 g, 2.49 mmol, 1.0 equiv) in 5 mL of THF is added dropwise over 10 min. The dropping funnel is rinsed with a small amount of THF. The mixture is stirred at room temperature for 2 h. The light orange mixture is hydrolyzed by adding methanol (1 mL). Most of the solvent is removed on a rotary evaporator until a slurry results. The slurry is diluted with petroleum ether (20 mL), and the supernatant solution is decanted and filtered. The filtrate is washed with water, dried over $MgSO_4$, filtered and concentrated to give the desired product (900 mg, 90%).

To compound 9 (800 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) is added *m*-CPBA (410 mg, 2.4 mmol, 1.2 equiv). Stirring is continued at room temperature for 2 h. The resulting mixture is washed with 10% Na_2SO_3, water and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography gives the desired product (740 g, 89%).

Module IV



(a) TMSCl, CH_2Cl_2, Et_3N, rt
(b) Ethylene oxide, CH_2Cl_2, rt, p-TsCl, pyridine

To a solution of amine **6** (500 mg, 2.59 mmol), in a suitable solvent such as CH_2Cl_2 (5 mL), is added trimethylsilyl chloride (1.55 g, 14.2 mmol, 5.5 equiv) followed by triethylamine (2.9 mL, 20.7 mmol, 8 equiv). The reaction mixture is stirred at room temperature for 6 h. Water is added to quench the reaction. The organic layer is washed with water, saturated NaCl and dried over anhydrous magnesium sulfate. The filtered solution is concentrated by rotary evaporation to obtain the silylated product, **11** (1.3 g, 91%).

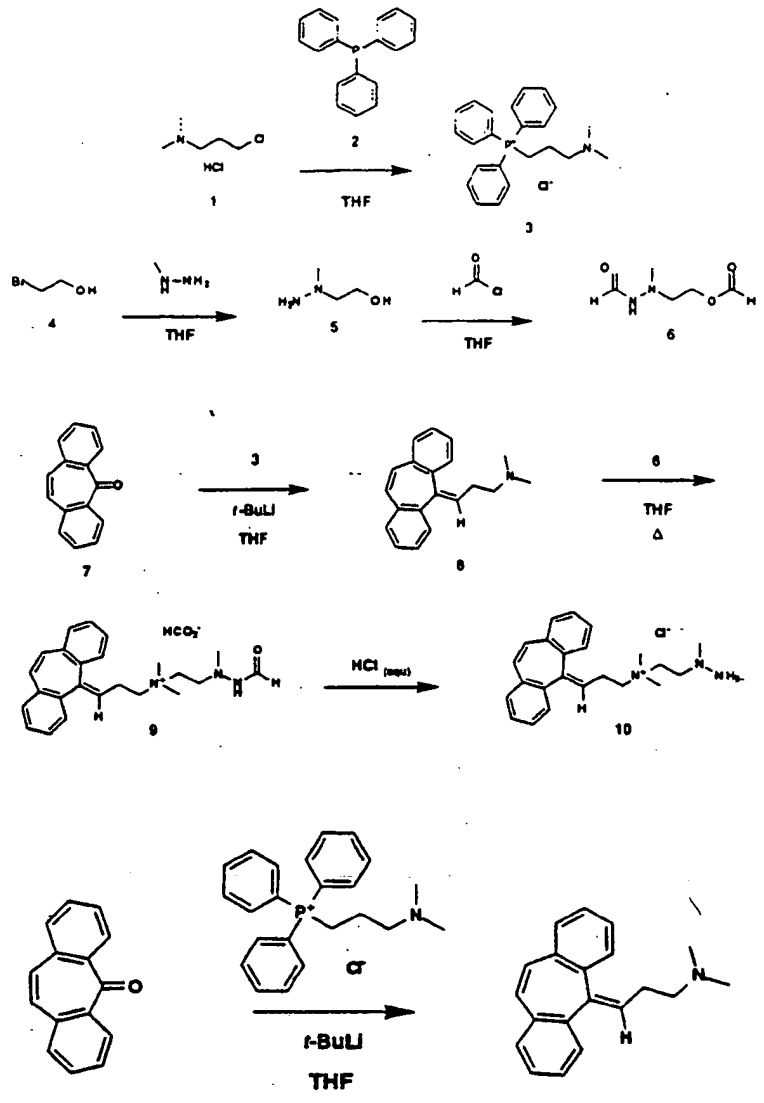
To a solution of **11** (1 g, 1.8 mmol), in a suitable solvent such as CH_2Cl_2 (10 mL), is added ethylene oxide (87 mg, 1.98 mmol, 1.1 equiv). After stirring 2 h at room temperature, *p*-toluenesulfonyl chloride (340 mg, 1.8 mmol, 1.0 equiv) and pyridine (280 mg, 3.6 mmol, 2 equiv) are added to the reaction mixture. Stirring continues for another 12 h. The organic layer is washed with water and saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The desired product, **12**, (1.1 g, 86%) is obtained by flash column chromatography.

Synthesis of pharmacophore containing modules for incorporation into aminimide backbone scaffold

As an illustration of the chemistry involved with the concepts mentioned above, the following examples are specific cases of the formation of monomeric units formed through linking pharmacophoric molecules to a hydrazino or hydrazido moiety for further modification or polymerization:

EXAMPLE 17.

Synthesis of *5H*-5-(*N,N*-Dimethyl-1-amino-3-propenyl)dibenzo[a,d]cycloheptene:

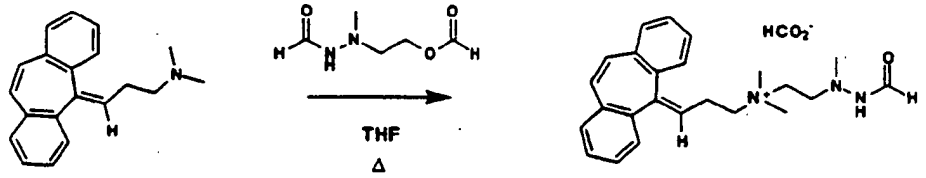


A solution of dimethylaminopropyltriphenylphosphonium chloride (23.4 g, 61.0 mmole, which is prepared from the reaction of triphenylphosphine and 3-dimethylaminopropyl chloride) in a suitable anhydrous solvent, such as THF (300 mL), is cooled at 0 °C while an equimolar amount of a strong base, such as *n*-butyllithium (2.5 M solution in hexanes, 25.0 mL, 62.5 mmol) is added dropwise with stirring over a period of 30 minutes. The reaction is stirred at room temperature for another hour. A solution of

dibenzosuberenone (12.5 g, 60.6 mmole) in an appropriate anhydrous solvent, such as THF (100 mL) is added dropwise, with stirring, over a period of 30 minutes. The reaction is stirred at 0 °C for another two hours, then quenched with the addition of water (150 mL), made basic such as with the addition of concentrated aqueous NaOH (10 mL). The volume of the resulting mixture is partially reduced *in vacuo*, then extracted with ether (2 x 150 mL). The combined organic layers are washed with saturated aqueous $NaHCO_3$ (2 x 150 mL), then brine (1 x 100 mL), dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation to afford 29 g of a yellow oil. The crude material is purified with column chromatography on a suitable stationary phase such as normal phase silica gel and eluted with an appropriate mobile phase, such as hexanes-ethyl acetate mixtures, to afford the desired compound (14.2 g, 85%). A portion is repurified to yield a sample for analysis.

EXAMPLE 18.

Synthesis of 5*H*-5-(*N*,*N*-Dimethyl-*N*-(2-(*N*-methyl-*N'*-formylhydrazino)-ethyl)-1-amino-3-propenyl)-dibenzo[a,d]cycloheptene formate:

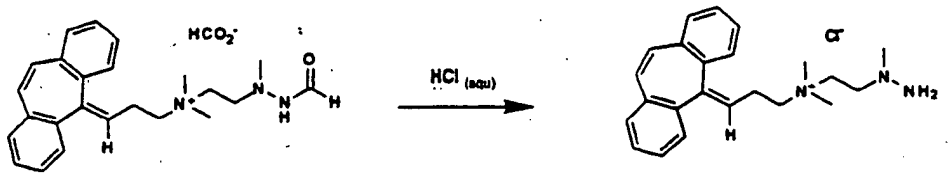


A solution of 5*H*-5-(*N*,*N*-Dimethyl-1-aminoprop-3-enyl)-dibenzo[a,d]cycloheptene (10.3 g, 37.4 mmol) in an anhydrous solvent, such as THF (100 mL), is stirred while *N*-(*N*-methyl-*N'*-formylhydrazino)-2-ethanol formate ester (5.47 g, 37.4 mmol, prepared from the reaction of 2 equivalents of formyl chloride with *N*-(*N*-methylhydrazino)-2-ethanol) is added. The reaction mixture is gently refluxed overnight. The solvent is evaporated, and the resulting residue is

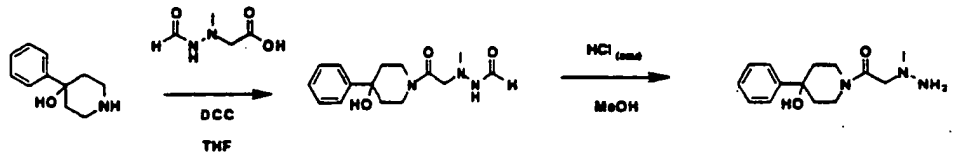
recrystallized. After filtration, the isolated solid is washed thoroughly and dried *in vacuo* to yield the desired product (14.9 g, 95%). A portion is repurified to yield a sample for analysis.

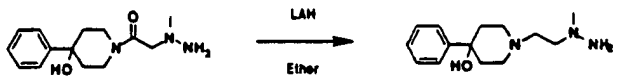
EXAMPLE 19.

Synthesis of 5*H*-5-(*N*,*N*-Dimethyl-*N*-(2-(*N*-methylhydrazino)-ethyl)-1-amino-3-propenyl)-dibenzo[a,d]cycloheptene chloride:



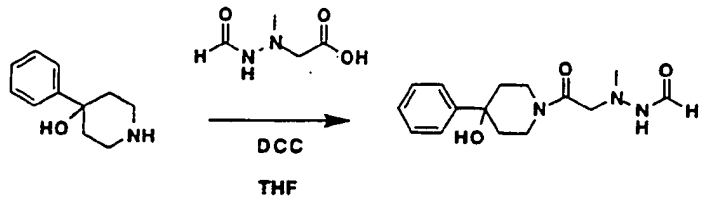
A solution of 5*H*-5-(*N*,*N*-Dimethyl-*N*-(2-(*N*-methyl-*N'*-formylhydrazino)-ethyl)-1-amino-3-propenyl)-dibenzo[a,d]cycloheptene formate (10.7 g, 25.4 mmol), dissolved in an appropriate solvent, such as methanol, with an equimolar amount of aqueous 0.5 N HCl, is stirred at 50 °C for 4 hours. The solvent is evaporated/lyophilized, and the resulting residue is recrystallized. After filtration, the isolated solid is washed thoroughly and dried *in vacuo* to yield the desired product (14.9 g, 95%). A portion is repurified to yield a sample for analysis.





EXAMPLE 20

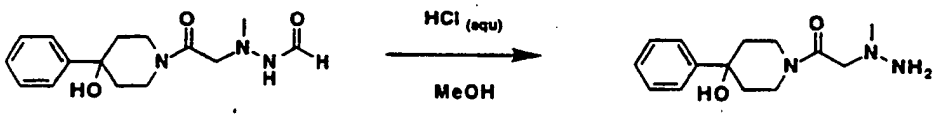
Synthesis of 4-Hydroxy-*N*-(*N*-(*N*-methyl-*N'*-formylhydrazino)ethan-2-amidyl)-4-phenylpiperidine:



A solution of *N*-(*N*-methyl-*N'*-formylhydrazino)-2-ethanoic acid (3.75 g, 28.4 mmol) in an anhydrous solvent, such as THF (100 mL), is stirred while *N,N'*-dicyclohexylcarbodiimide (x mg, x mmol) is added. The reaction is stirred for three minutes, then 4-hydroxy-4-phenylpiperidine (5.00 g, 28.2 mmol) in an appropriate solvent, such as THF (100 mL), is added. Dicyclohexylurea precipitates almost immediately. The resultant suspension is stirred for at least one hour, filtered to remove the insoluble urea. The solvent is removed on a rotary evaporator to afford an off white solid (7.48 g, 91%). Recrystallization of a portion gives a sample for analysis.

EXAMPLE 21

Synthesis of 4-Hydroxy-*N*-(*N*-(*N*-methylhydrazino)-2-ethanamidyl)-4-phenylpiperidine.

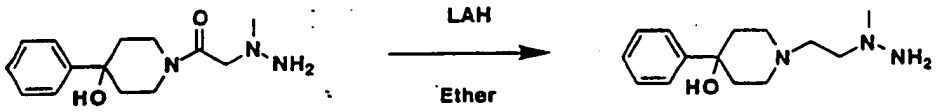


A solution of 4-hydroxy-*N*-(*N*-(*N*-methyl-*N'*-formylhydrazino)-2-ethanamidyl)-4-phenylpiperidine (6.03 g, 20.7 mmol) dissolved in an appropriate solvent such as methanol/water or THF/water, with an equimolar amount of aqueous).5 N HCl is stirred at 50 °C for 4 hours. The mixture is treated with Amberlite IR-45 resin. The mixture is filtered, and the filtrate evaporated/lyophilized to afford the desired

product as a solid (5.38 g, 99%). A portion is recrystallization to give a sample for analysis

EXAMPLE 22

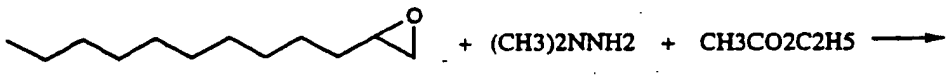
Synthesis of 4-Hydroxy-*N*-(*N*-(*N*-methylhydrazino)-eth-2-yl)-4-phenylpiperidine.

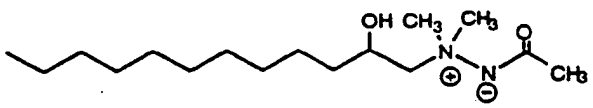


Lithium aluminum anhydride (1.87 g, 49.3 mmole) is added, slowly, to a stirring solution of 4-hydroxy-*N*-(*N*-(*N*-methylhydrazino)-2-ethanamidyl)-4-phenylpiperidine in a suitable anhydrous solvent, such as THF or diethyl ether (100 mL), at 0 °C. The mixture is allowed to stir for an hour at room temperature, then cooled to 0 °C. Ethyl acetate (40 mL) is added, with vigorous stirring, to quench the reaction, followed by the careful addition of a saturated aqueous solution of sodium sulfate to neutralize the mixture. The white aluminum salts are filtered, and washed thoroughly with an appropriate solvent such as diethyl ether or ethyl acetate. The filtrate is concentrated on a rotary evaporator to yield the desired product as a solid (3.63 g, 89%). A portion is recrystallization to give a sample for analysis.

EXAMPLE 23

Synthesis of an Aminimide Amphiphile: 1,1-dimethyl-1-(2-hydroxydodecyl)-2-acetylhydrazinium inner salt.

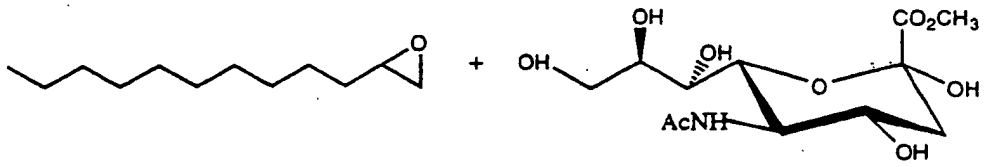


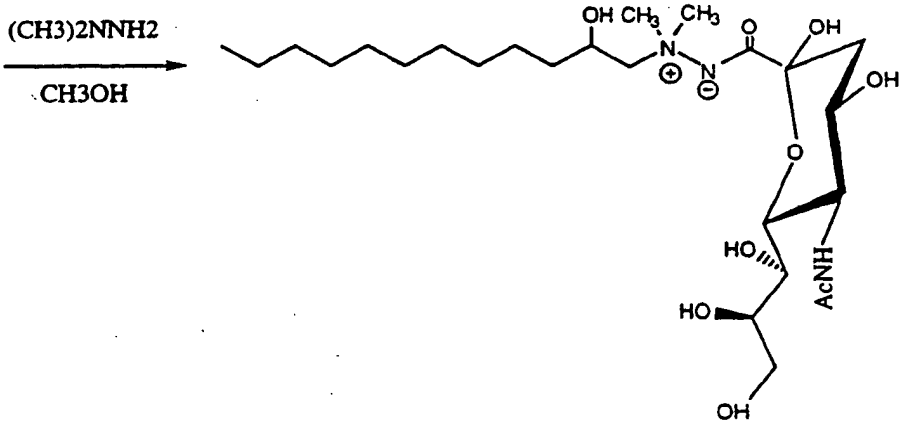


1,1-Dimethyl-1,1-(2-hydroxydodecyl)-2-acetyl hydrazinium inner salt (29.0 g, 0.1 mol) and 1-iodododecane (29.5 g, 0.11 mol) were dissolved in benzene (300 mL). Anhydrous K_2CO_3 (20.7 g, 0.15 mol) was added and the mixture refluxed for 12 hours. The solids were removed by filtration and the volatile components were removed *in vacuo* at 0.1 torr for 24 hours to give a waxy solid (44.2 g, 99%). The product was characterized by ^{1}H-NMR and FTIR.

EXAMPLE 24

Synthesis of a Sialic Acid-Derivitized Aminimide Amphiphile Conjugate



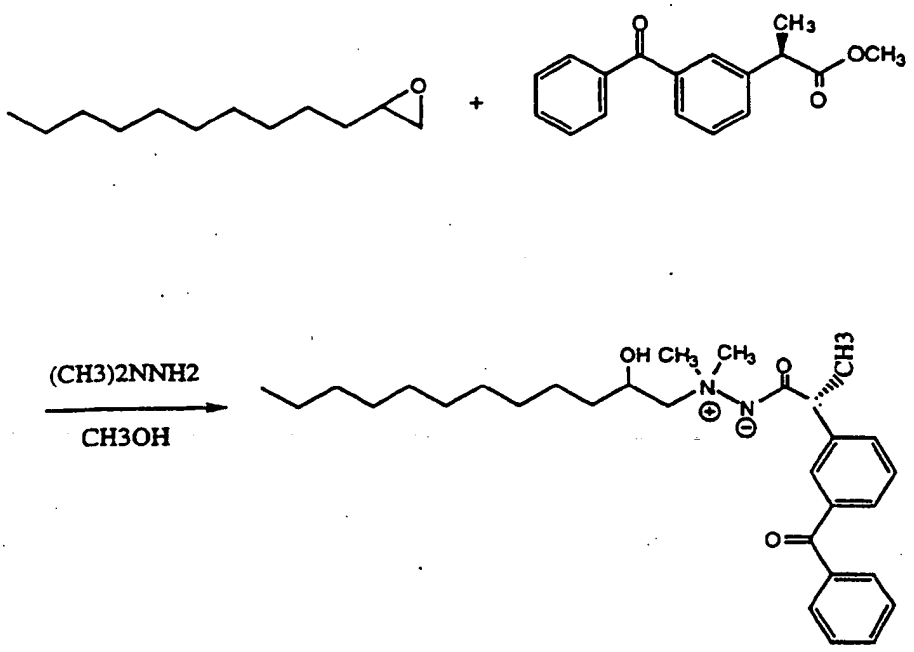


1,2-Epoxydodecane (2.68g, 0.01 mol), 1,1-dimethylhydrazine (0.6 g, 0.01 mol) and sialic acid methyl ester (3.23 g, 0.01 mol) are dissolved in methanol (50 mL). The resulting clear yellow solution is stirred at room temperature

for 96 hours. The solution was concentrated on a rotary evaporator *in vacuo*, then subjected to vacuum (0.1 torr), to remove any residual solvent, leaving a quantitative yield of the waxy solid sialic acid derivative, characterized by ^{1}H-NMR and FTIR spectroscopy.

EXAMPLE 25.

Synthesis of a Ketoprofen-Derivitized Aminimide Amphiphile Conjugate



1,2-Epoxydodecane (26.75 g, 0.1 mol), 1,1-dimethylhydrazine (6.01 g, 0.1 mol), and S-ketoprofen (26.8 g, 0.1 mol) were dissolved in 150 mL of methanol. The resulting clear yellow solution was stirred at room temperature for 96 hours. The solution was concentrated on a rotary evaporator *in vacuo*, then subjected to vacuum (0.1 torr) to remove any residual solvent, leaving a waxy solid ketoprofen aminimide derivative (59.23 g), characterized by its ^{1}H-NMR and FTIR spectra.

EXAMPLE 26

Synthesis of an Aminimide Lipid Mimetic

1,2-Epoxydodecane (26.75 g, 0.145 mol), 1,1-dimethylhydrazine (8.72 g, 0.145 mol) and ethyl acetate (12.78 g, 0.145 mol) were dissolved in methanol (50 mL). The resulting clear yellow solution was stirred at room temperature for 96 hours. The solution was concentrated on a rotary evaporator *in vacuo*, then subjected to vacuum (0.1 torr) to remove any residual solvent. The resulting thick glass was cooled to 0 °C and scratched with a glass rod to initiate crystallization. The crystalline aminimide (39.22 g, 93%) was obtained and characterized by its ^{1}H-NMR and FTIR spectra.

EXAMPLE 27.

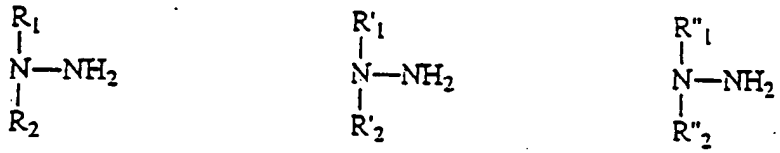
Synthesis of a Ketoprofen Lipid Mimetic

1,1-dimethyl-1,1-(2-hydroxydodecyl)-2-ketoprofen-hydrazinium inner salt (3.23 g, 0.01 mol), prepared as described above, and 1-iodododecane (2.95 g, 01.1 mol) is dissolved in benzene (30 mL). Anhydrous K_2CO_3 (2.07 g, 0.015 mol) was added. The mixture was refluxed for 12 hours. The solids were removed by filtration, and the volatile components were removed *in vacuo* at 0.1 torr for 24 hours to give a waxy solid product (4.4. g, 98%). The product is characterized by ^{1}H-NMR and FTIR.

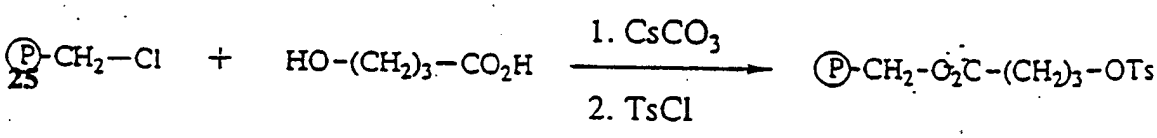
EXAMPLE 28.

Synthesis of 27-mer combinatorial library

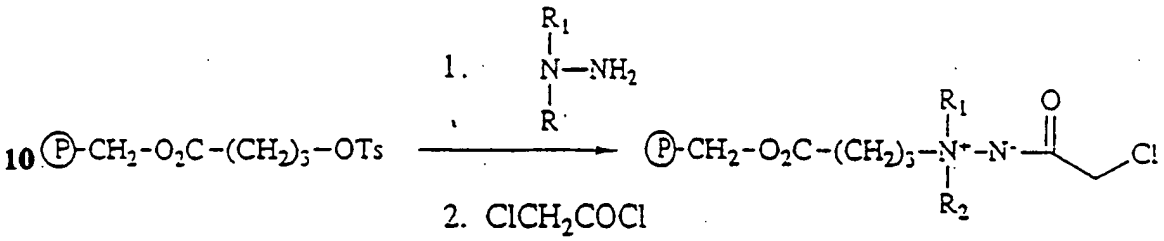
The following is one of the many methods that are being contemplated for use in constructing random combinatorial libraries of aminimides-based compounds; the random incorporation of three aminimides derived from α-chloroacetyl chloride and the hydrazines shown below to produce 27 trimeric structures linked to the support via a succinoyl linker is given below:



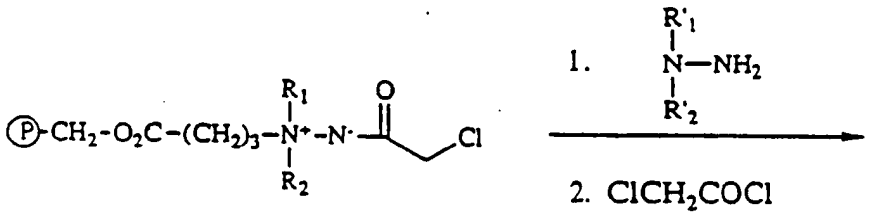
(1) A suitable solid phase synthesis support, e.g., the chloromethyl resin of Merrifield is treated with 4-hydroxyl butyric acid in the presence of Cs_2CO_3 followed by tosylation with *p*-toluenesulfonyl chloride, under conditions known in the art:

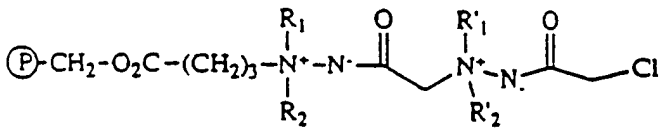


(2) The resulting resin is divided into three equal portions. Each portion is coupled with one of the hydrazines shown above to give the hydrazinium resin which is converted to the aminimide by reaction with chloroacetyl chloride using the experimental conditions described above.

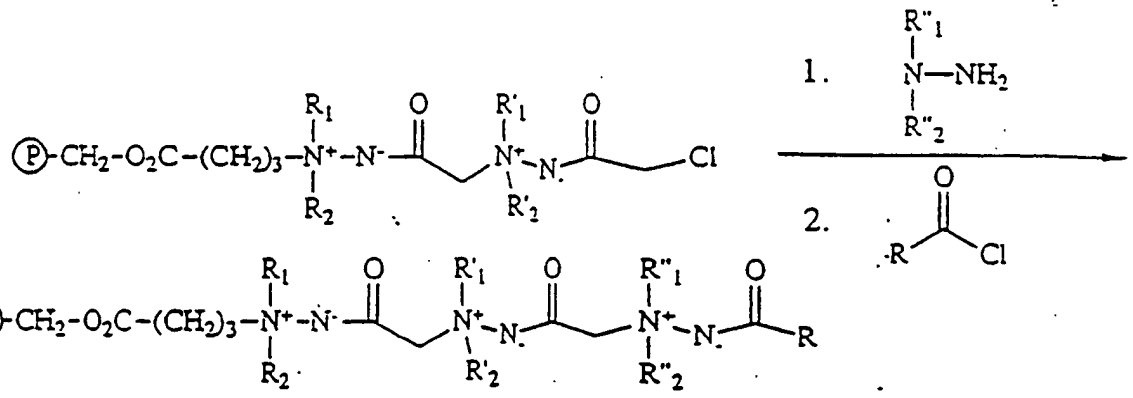


(3) The aminimide resin portions are mixed thoroughly and divided again into three equal portions. Each resin portion is coupled with a different hydrazine followed by a coupling with α-chloracetyl chloride producing a resin with two linked aminimide subunits. The resin portions are then mixed thoroughly and divided into three equal portions.



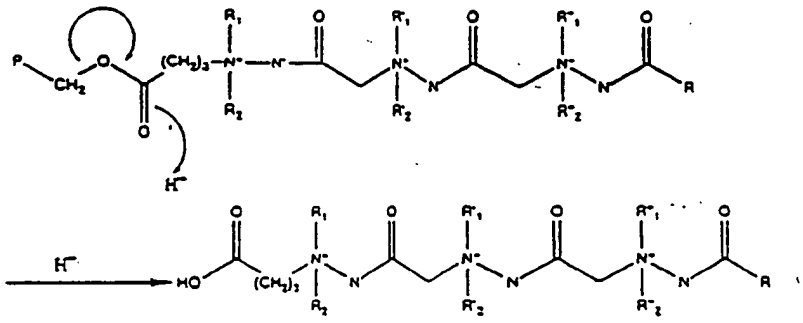


(4) Each resin portion is coupled with a different hydrazine followed by reaction with an acid chloride to produce a resin with three linked aminimide subunits:



The resin portions are mixed producing a library containing 27 types of beads each bead type containing a single trimeric aminimide species for screening using the bead-stain method described above. Alternatively, the aminimides may be detached from the support via acidolysis producing a "solution-phase" library of aminimides containing a butyrylated terminal nitrogen, shown in the structure below in which R = C_3H_7):

FORMULA 11A

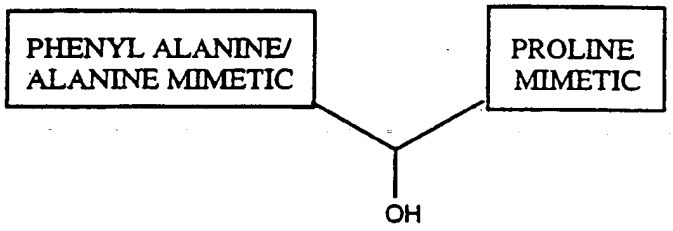


EXAMPLE 29.

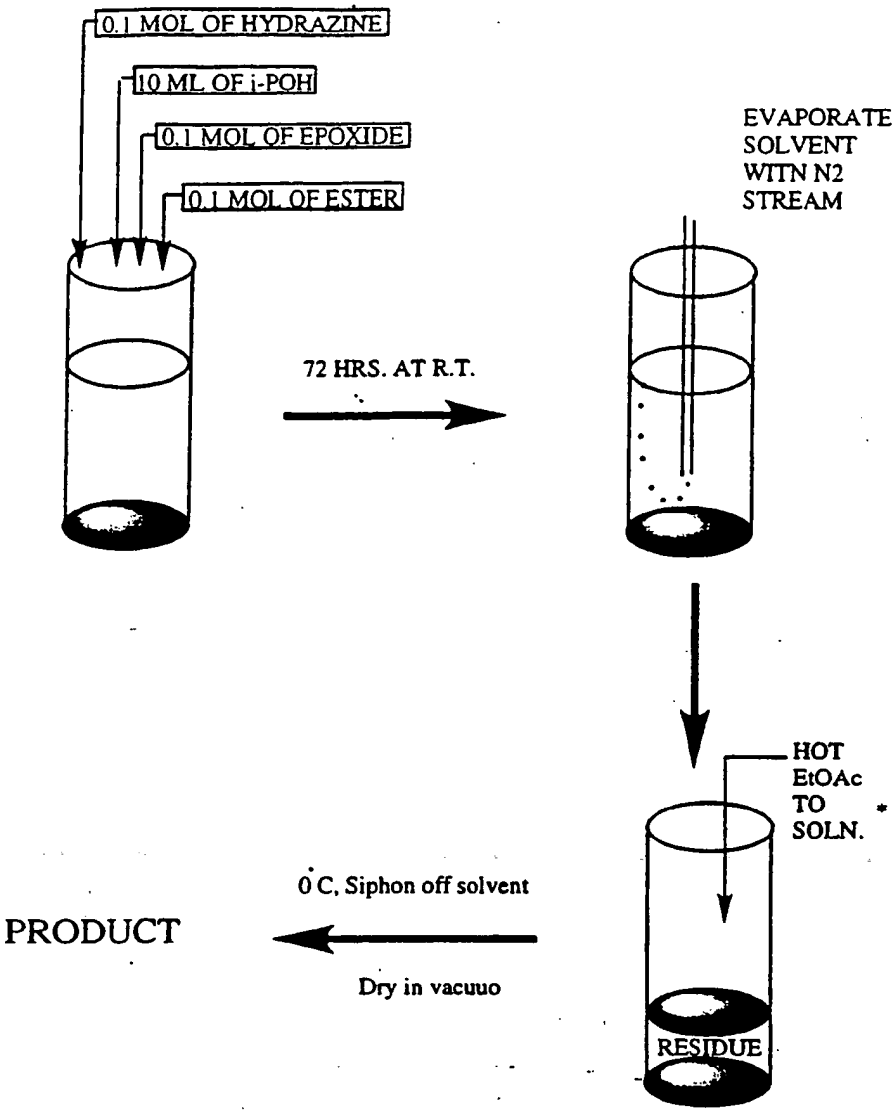
Thematic Combinatorial Aminimide Library

The following example outlines the generation of a matrix of 16 molecules around the basic structural theme of a hydroxy-proline transition state mimetic inhibitor for proteases:

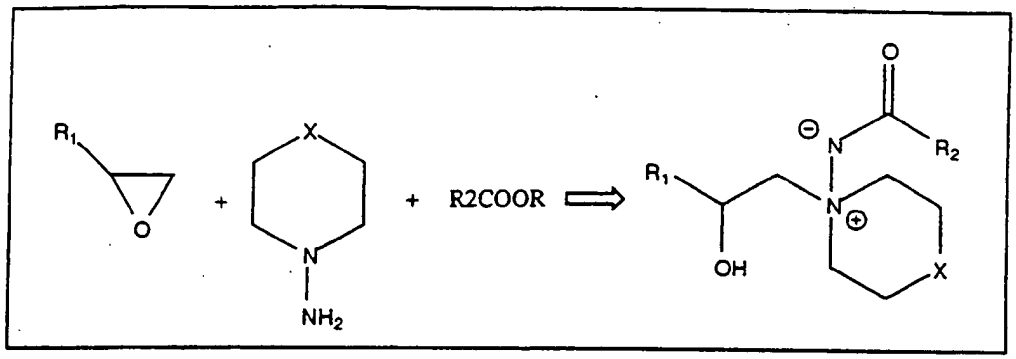
Structural Theme:



This mimetic was synthesized by reacting styrene oxide or propylene oxide, ethyl acetate or methyl benzoate with four commercially available cyclic hydrazines (as mimetics of proline) in isopropanol in 16 individual sample vials, as shown below:



* Four of the residues did not completely dissolve



X = CH2		X = NMe		X = O		X = CH2CH2	
R1	R2	R1	R2	R1	R2	R1	R2
Ph	Me	Ph	Me	Ph	Me	Ph	Me
Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph
Me	Me	Me	Me	Me	Me	Me	Me
Me	Ph	Me	Ph	Me	Ph	Me	Ph

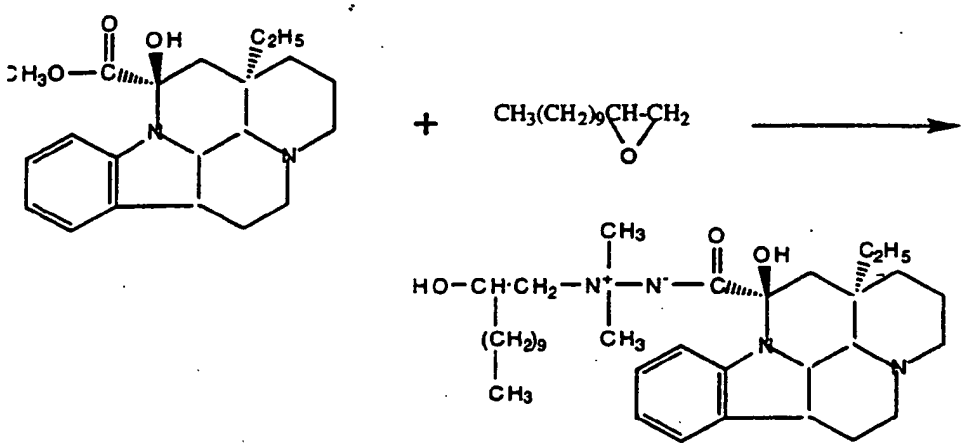
These 16 materials were isolated in essentially quantitative yield on removal of the reaction solvent by evaporation and purified samples were obtained as crystalline solids after recrystallization from ethyl acetate and characterized by ^{1}H-NMR, FTIR and other analytical techniques.

EXAMPLE 30.

Synthesis of an amphiphillic ligand useful in the isolation and pudrification of receptors binding vincamine:

To a solution of 1,2-epoxydodecane (I) (1.84 g, 0.01 mol) in a suitable solvent, such as *n*-propanol, is added, with stirring, 1,1-dimethylhydrazine (0.61 g, 0.01 mol). The solution is stirred for 1 hour at room temperature, cooled to 10 °C in an

ice bath, and a solution of vincamine (II) (3.54 g, 0.01 mol), dissolved in the minimum amount of the same solvent, is added. The reaction mixture is stirred at 0 °C for 2 hours, then stirred at room temperature for 3 days. The solvent is removed under high vacuum (0.2 torr) and the crude product is isolated. The conjugate (II) is useful as a stabilization agent for the isolation and purification of receptor proteins which are acted upon by vincamine and structurally related molecules.

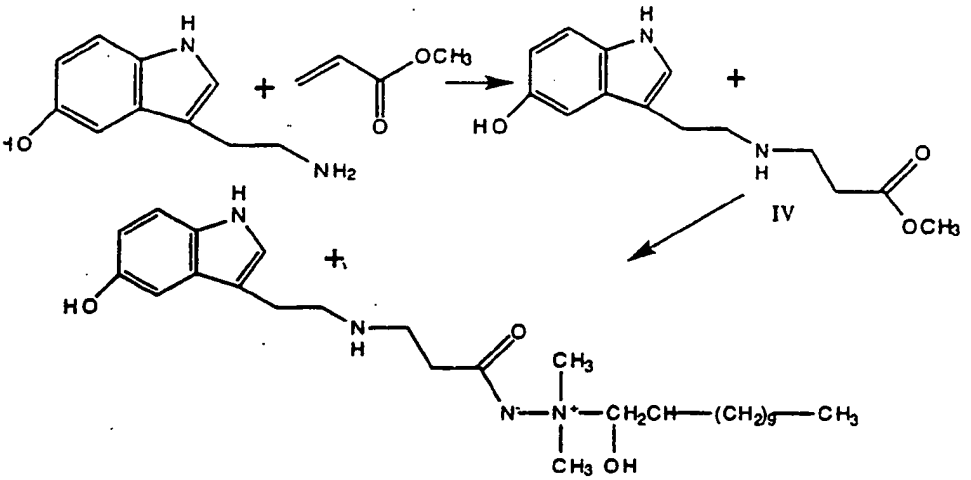


EXAMPLE 31

Synthesis of an amphiphillic ligand useful in the isolation and purification of serotonin binding receptors

Methyl acrylate (8.61 g, 0.1 mol) is added over a 15 minute period to a stirring solution of serotonin (17.62 g, 0.1 mol) in a suitable solvent (100 mL). The reaction mixture is stirred at room temperature for 2 days. The solvent is removed by freeze drying to yield the ester (IV). 1,1-Dimethylhydrazine (6.01 g, 0.1 mol) is added, with stirring, to a solution of 1,2-epoxydodecane (18.4 g, 0.1 mol) in a suitable solvent, such as propanol. The mixture is stirred at room temperature for 1 hour and a solution of (IV), dissolved in the same solvent, is added. The mixture is continued for 3 days. The solvent is removed *in vacuo* to yield the serotonin conjugate (V), which is useful as a ligand for the discovery,

stabilization and isolation of serotonin-binding membrane receptor proteins.



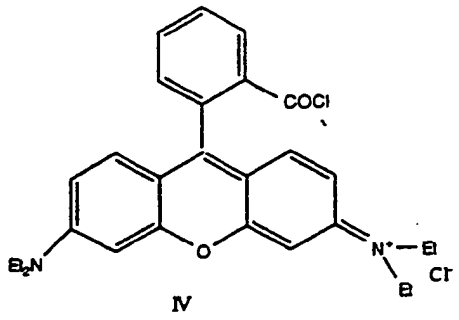
EXAMPLE 32.

Synthesis of a rhodamine-B containing ligand mimetic useful in the isolation and purification of codeine-binding proteins:

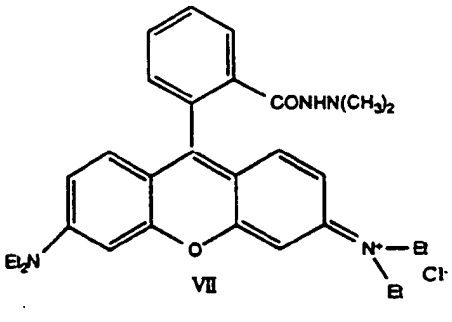
The acid chloride of Rhodamine B (VI) (49.74 g, 0.1 mol, prepared from rhodamine B by the standard techniques for preparing acid chlorides from carboxylic acids), dissolved in a suitable solvent (500 mL), are added, with stirring, over a 1-hour period to a solution of 1,1-dimethylhydrazine (6.01 g, 0.1 mol) in 100 mL of the same solvent. The temperature is kept at 10 °C. After the addition is complete, the mixture is stirred at room temperature for 12 hours, and the solvent is removed *in vacuo* to yield the Rhodamine B dimethylhydrazine (VII).

The Rhodamine B dimethylhydrazine (VII) (5.21 g, 0.01 mol) is dissolved in a suitable solvent, such as benzene (100 mL), and tosyl codeine (VIII) (4.69 g, 0.01 mol, prepared from codeine by the standard techniques for the tosylation of an alcohol), in 50 mL of the same solvent are added over a 15 minute period, with stirring. The mixture is refluxed for 1 hour. The mixture is then cooled, the solvent is removed *in vacuo*, the residue is redissolved in an appropriate alcohol and

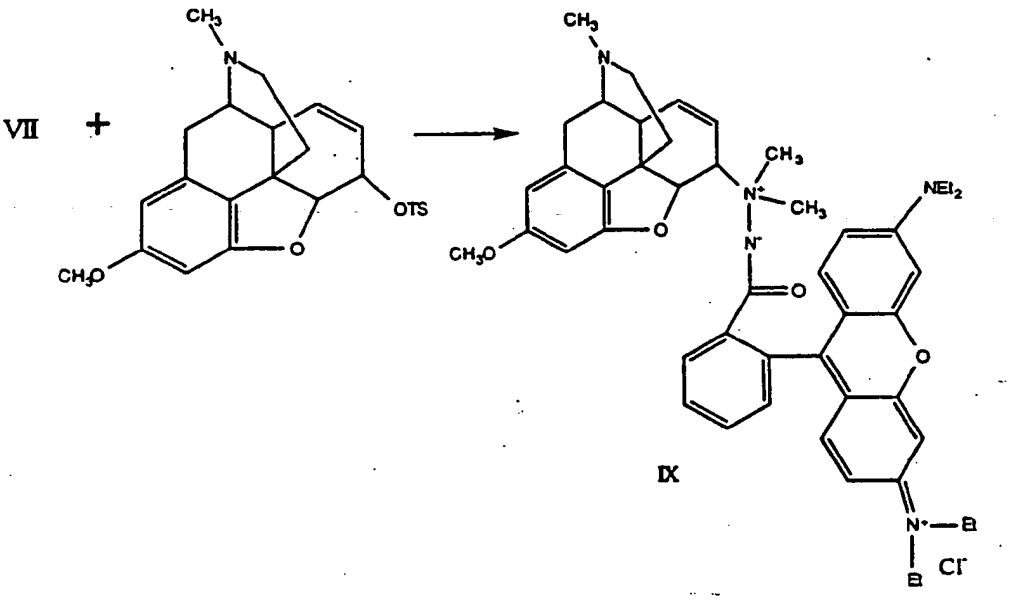
adjusted to pH 8 with 10% methanolic KOH. The precipitated salts are removed by filtration. The solvent is removed *in vacuo* to yield the conjugate (IX), useful as a probe for the location, stabilization and isolation of receptor proteins that bind codeine and structurally similar analogs.



IV



VII

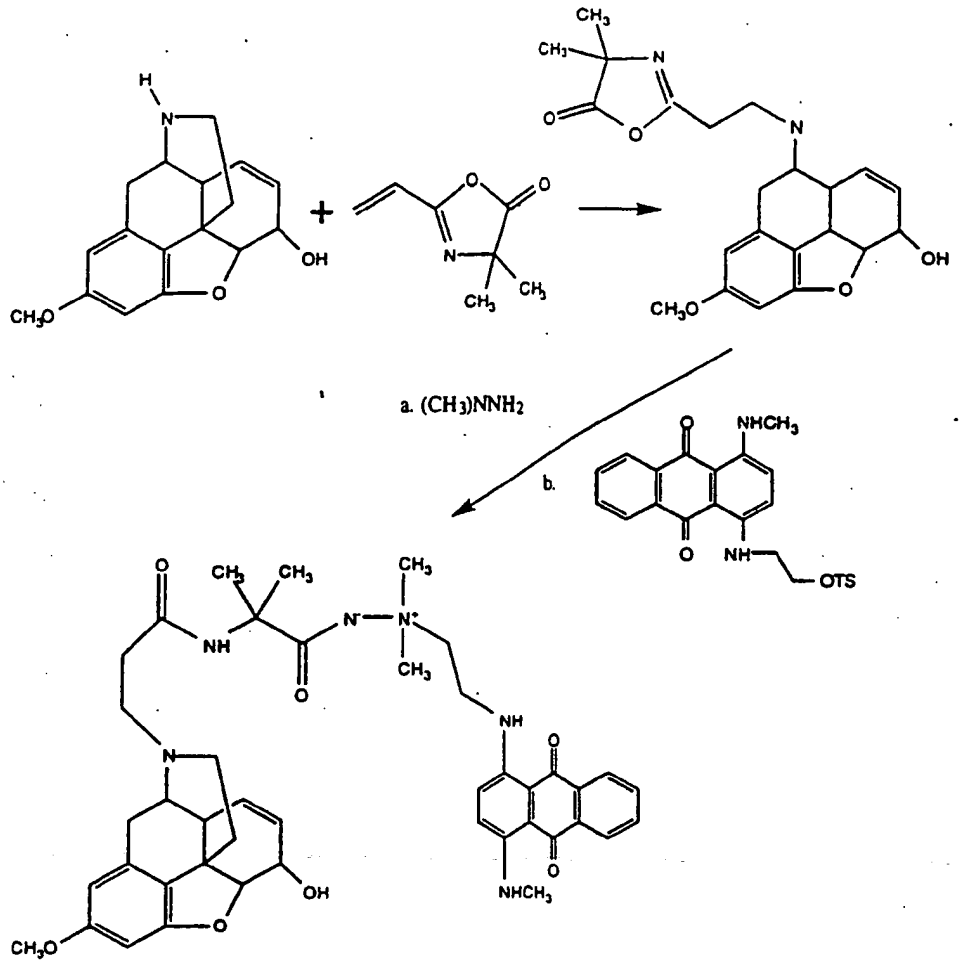


EXAMPLE 33.

Synthesis of a disperse-blue-3 containing ligand useful in the isolation and purification of codeine-binding proteins

To a solution of norcodeine (X) (0.285 g, 0.001 mol), dissolved in a suitable solvent, such as benzene (50 mL), is added a solution of 4,4'-dimethylvinylazlactone (XI) (0.139 g,

0.001 mol) in 10 mL of the same solvent. The resulting solution is heated to 70 °C for 10 hours. The temperature is brought to 10 °C with cooling and 1,1-dimethylhydrazine (0.06 g, 0.001 mol) dissolved in 10 mL of the same solvent is added dropwise. The solution is reheated to 70 °C for 2 hours. Disperse blue 3 tosylate (XII) (0.466 g, 0.001 mol, prepared by the standard tosylation techniques from a pure sample of the dye obtained from the commercial material by standard normal-phase silica chromatography), is added and the mixture is heated at 70 °C for 2 more hours. The solvent is removed *in vacuo*, the residue is redissolved in an appropriate alcohol solvent and titrated to pH 8 (measured with moist pH paper) with 10% (w/v) methanolic KOH. The precipitated salts are then removed by filtration. The filtrate is concentrated *in vacuo* to give conjugate (XIII), useful as a probe for the location and isolation of receptor proteins that bind codeine and similar molecules.



EXAMPLE 34.

Synthesis of an amphiphillic ligand for the isolation and purification of codeine-binding proteins:

Octadecylisocyanate (29.95 g, 0.1 mol) is added slowly to 1,1-dimethylhydrazine (6.01 g, 0.1 mol) in benzene (100 mL). The mixture is stirred for 18 hours at room temperature, and tosyl codeine (VIII) (54.2 g, 0.1 mol, prepared by the standard techniques), is added portionwise over a 1/2 hour period. The mixture is stirred and refluxed for 2 hours. The solvent is removed *in vacuo*, the residue is dissolved in an appropriate solvent (such as ethanol), and the pH is titrated to 8 (measured with moist pH paper) with 10% (w/v) methanolic KOH. The precipitated salts are removed by

filtration. The solvent is removed *in vacuo* to give the crude conjugate (XIV), useful for stabilizing and isolating receptor proteins that bind to codeine and to similar molecules.

EXAMPLE 35.

Synthesis of a mimetic of a protein kinase binding peptide

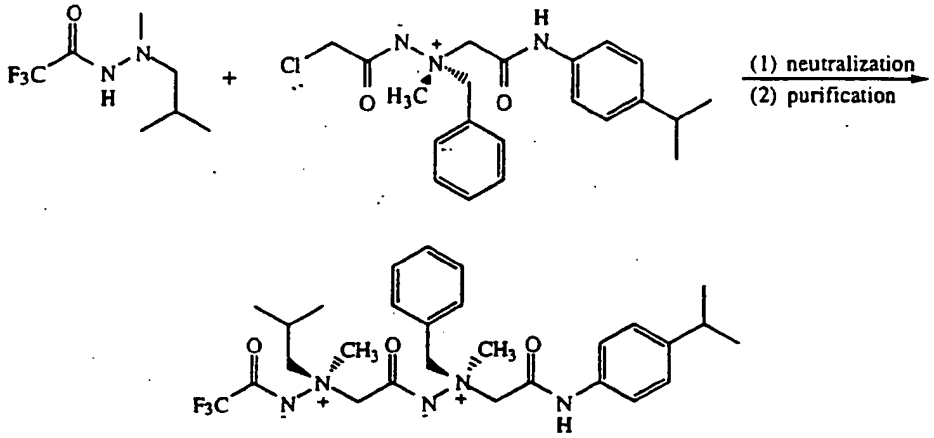
a. The dodecamer peptide (BEAD)-Asp-His-Ile-Ala-Asn-Arg-Arg-Gly-Thr-Arg-Gly-Ser-NH_2 is attached to the solid support as shown using standard FMOC peptide synthesis techniques, after deprotection of the terminal FMOC group. This peptide is shaken with a solution of an equivalent molar amount of $ClCH_2COCl$ in a suitable solvent at 50 °C for 6 hours. The solvent is removed by decanting, leaving a terminal -NH-CO-CH_2Cl group attached to the peptide.

b. A solution of equimolar amounts of 1,1-dimethylhydrazine and *N,N'*-dicyclohexylcarbodiimide, in a suitable solvent, is treated with an equivalent molar amount of the heptamer peptide H_2N-Thr-Thr-Tyr-Ala-Asp-Phe-Ile-COOH, prepared and obtained in the free state using the standard FMOC solid phase peptide synthesis chemistry (e.g., using instruments and methods marketed by the Milligen Division of Millipore Corp.). The mixture is stirred for 4 hours at room temperature. The precipitated N,N'-dicyclohexylurea is removed by centrifuging and decanting, and the solution is added to the functionalized beads prepared in a. above. The mixture is heated to 50 °C and shaken overnight. After cooling, the solvent is removed by decanting, and the peptide is released from the bead to yield the aminimide mimetic H_2N-Thr-Thr-Tyr-Ala-Asp-Phe-Ile-CO-N-N$(CH_3)_2$-CH_2-Ser-Gly-Arg-Thr-Gly-Arg-Asn-Ala-Ile-His-Asp-COOH. This mimetic has the aminimide in place of alanine in the naturally occurring protein-kinase binding peptide, UK (5-24), and is useful as a synthetic binding peptide with enhanced proteolytic stability.

EXAMPLE 36

Synthesis of a mimetic of an elastase inhibitor

This example teaches the synthesis of a competitive inhibitor for human elastase based on the structure of known N-trifluoroacetyl dipeptide analide inhibitors (see 162 J. Mol. Biol. 645 (1982) and references cited therein).

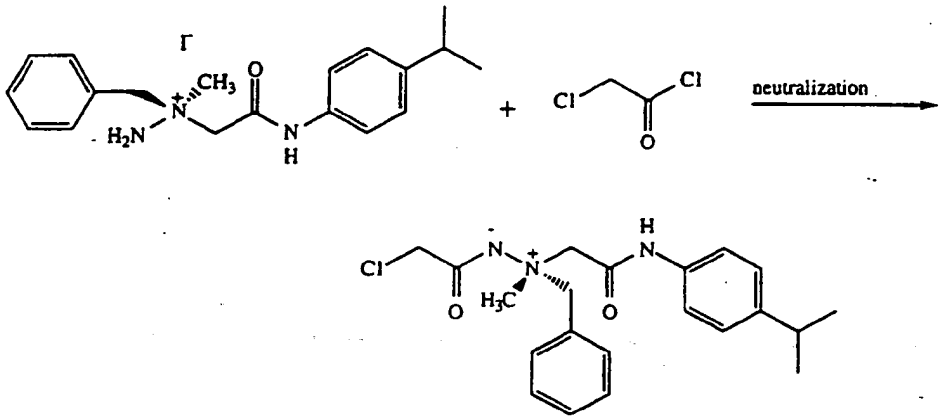


The aminimide N-(p-isopropylanalido)-methyl)-S-N-methyl-N-benzylchloromethylacetamide (3.7 g, 0.01 mol) in ethanol (50 mL), and 1-methyl-1-isobutyl-2-N-trifluoroacetyl hydrazide (1.86 g, 0.01 mol, prepared from the reaction of trifluoroacetic anhydride with 1-methyl-1-isobutylhydrazine [from methylisobutylamine and chloramine] using standard acylation methods) in ethanol (50 mL) were combined. The mixture was stirred and refluxed for 4 hours. The mixture was cooled to room temperature and titrated with 10% (w/v) KOH in methanol to the phenolphthalein endpoint. The mixture was then filtered and the solvent removed *in vacuo* on a rotary evaporator. The residue was taken up in benzene and filtered. Removal of the benzene on the rotary evaporator yielded a crude mixed diastereomeric aminimides (5.1 g, 95%). The desired (S)-(S) isomer was obtained by normal-phase chromatographic

purification over silica. This product is useful as a competitive inhibitor for human elastase, characterized by HPLC on Crownpack™ CR(+) chiral stationary phase (Daicell Chemical Industries Ltd.) using pH 2 aqueous mobile phase. ^{1}H-NMR (DMSO-d_6): Chemical shifts, peak integrations and D_2O exchange experiments diagnostic for structure.

EXAMPLE 37

Synthesis of the Chiral Chloroaminimide Starting Material

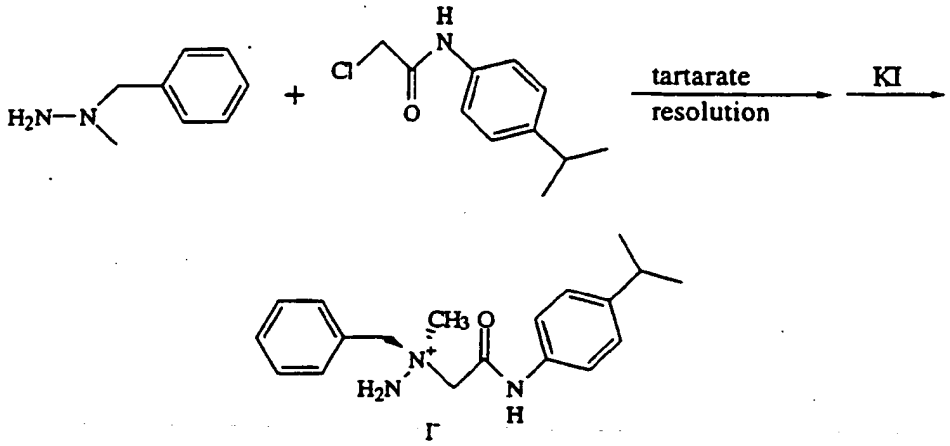


A mixture of the hydrazinium iodide enantiomer (4.2 g, 0.01 mol, prepared as outlined below), chloroacetic acid (1.0 g, 0.0106 mol) and chloracetyl chloride (1.24 g, 0.011 mol), contained in a micro reaction flask equipped with a drying tube, was heated in an oil bath to 105°C for 1 hour. The homogeneous reaction mixture was cooled to room temperature and extracted with diethyl ether (4 x 20 mL), to remove chloracetyl chloride and chloroacetic acid, with vigorous stirring each time. The residual semi-solid was dissolved in the minimum amount of methanol, and titrated with 10% KOH in methanol to the phenolphthalein end point. The precipitated salts were filtered and the filtrate evaporated to dryness on a rotary evaporator at 40 °C. The residue was taken

up in benzene and filtered. The solvent was removed on a rotary evaporator t yield the (S)-aminimide enantiomer (3.37 g, 90%), characterized by its $CDCl_3$ ^1H-NMR spectrum, D_2O exchange experiments and directly used in the next step in the sequence (see above).

EXAMPLE 38

Synthesis of the Chiral Aminimide Starting Material

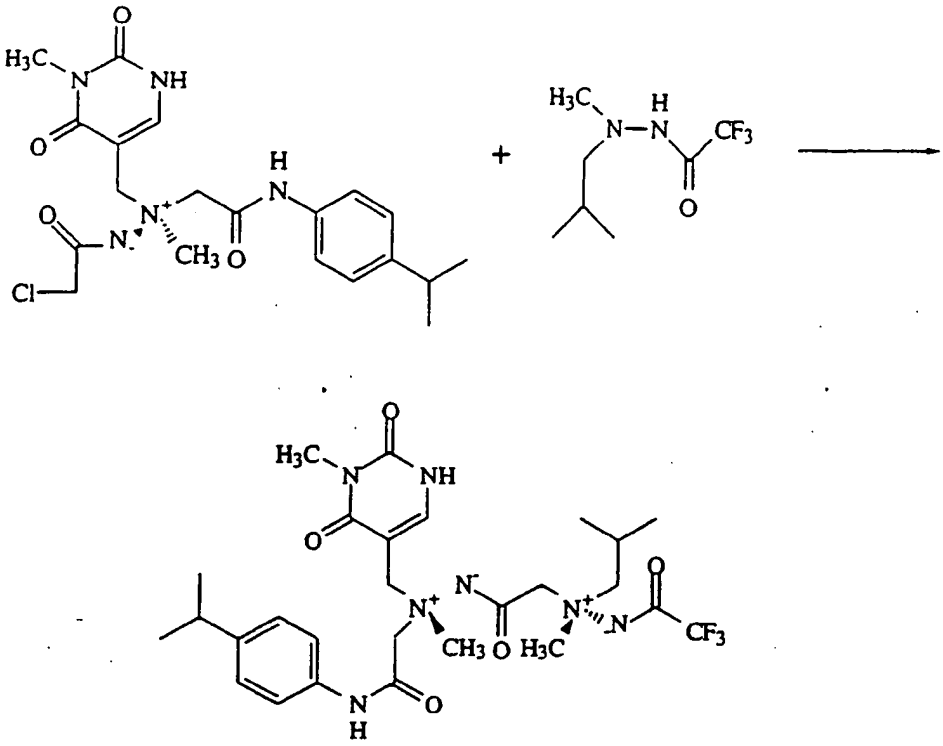


1-methyl-1-benzyl-hydrazine (13.6 g, 0.1 mol, prepared from methyl benzyl amine and chloramine using standard methods [J. Chem. Ed. 485 (1959)]) in toluene (125 mL) was cooled to 5 °C in an ice bath. To this solution was gradually added, with vigorous stirring over a one hour period. a solution of *p*-isopropylphenyl chloromethyl analide (21.17 g. 0.1 mol, prepared from chloracetyl chloride and *p*-isopropylphenyl amine) dissolved in toluene (100 mL). Throughout the addition, the temperature was maintained at 5 °C. The reaction mixture was stirred overnight at room temperature. The precipitated solid hydrazinium salt was filtered, washed with cold toluene and dried in a vacuum oven at 60 °C/30" to yield the racemic product (34.3 g, 98%) . This racemate was slurried at room temperature overnight in

ethanol (100 mL), and a slight molar excess of moist silver oxide was added. The mixture was again stirred at room temperature overnight. The mixture was filtered into an ethanolic solution containing an equivalent of D-tartaric acid in the minimum amount of solvent. The alcoholic filtrate was concentrated to approximately 20% of its volume and diethyl ether was added until turbidity was observed. The turbid solution was cooled at 0 °C overnight and the crystals were collected by filtration. The solid substance was purified by recrystallization from ethanol/ether to yield the desired pure diastereomeric salt, which was subsequently converted to the iodide form by precipitation from a water-ethanol solution of the tartrate (made alkaline by the addition of sodium carbonate) on treatment with an equivalent of solid potassium iodide, characterized by HPLC on Crownpack™ CR(+) chiral stationary phase (Daicell Chemical Industries Ltd.) using pH 2 aqueous mobile phase. ^{1}H-NMR (DMSO-d_6): chemical shifts, peak integrations & D_2O exchange experiments were diagnostic for the title structure.

EXAMPLE 39.

Synthesis of a peptidomimetic elastase inhibitor

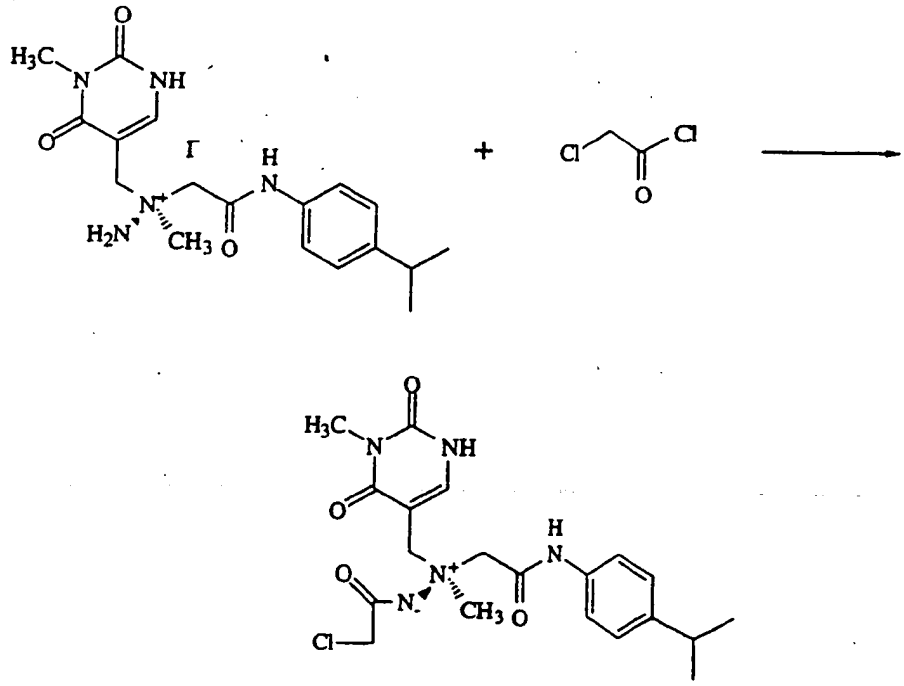


To a solution of the chloromethylaminimide (4.36 g, 0.01 mol), as prepared above, in ethanol (50 mL) was added a solution of 1-methyl-1-isobutyl-2-*N*-trifluoroacetylhydrazide (1.86 g, 0.01 mol, prepared from the reaction of trifluoroacetic anhydride with 1-methyl-1-isobutylhydrazine [from methyl isobutyl amine and chloramine] using standard acylation conditions) in ethanol (50 mL). The mixture was refluxed with stirring for 4 hours, cooled to room temperature then titrated with 10% (w/v) KOH in methanol to the phenolphthalein endpoint. The mixture was filtered, and the solvent was removed *in vacuo* on a rotary evaporator. The residue was taken up in benzene and again filtered. Removal of the benzene on the rotary evaporator yielded the mixed (R)-(S) and (S)-(S) aminimide diastereomers (5.7 g, 95%). The desired (S)-(S) isomer was obtained pure by normal-phase chromatographic purification over silica. This product is useful as a competitive inhibitor for human elastase, characterized by

HPLC on Crownpack™ CR(+) chiral stationary phase (Daicell Chemical Industries Ltd.) using pH 2 aqueous mobile phase. ^{1}H-NMR (DMSO-d_6): chemical shifts, peak integrations & D_2O exchange experiments were diagnostic for the desired structure.

EXAMPLE 40.

Synthesis of the Chiral Chloroaminimide.

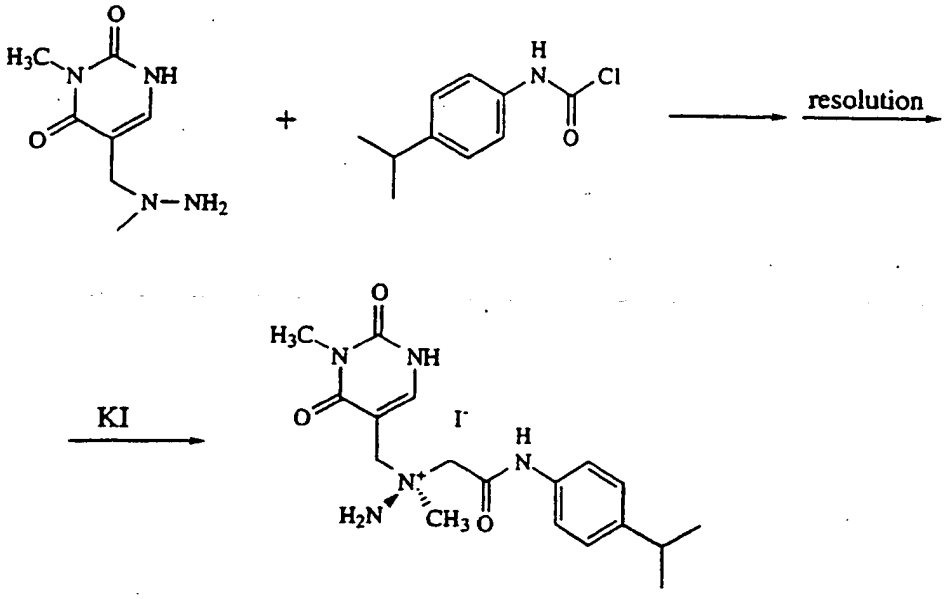


A mixture of the hydrazinium iodide enantiomer (4.87 g, 0.01 mol, prepared as described in 5.2.3), chloroacetic acid (1.0 g, 0.0106 mol) and chloroacetyl chloride (1.24 g, 0.011 mol), contained in a micro reaction flask equipped with a drying tube, was heated to 105 °C for 1 hour with an oil bath. The homogeneous reaction mixture was cooled to room temperature, then extracted with diethyl ether (4 x 20 mL) to remove chloracetyl chloride and chloroacetic acid. The residual semi-solid mass was dissolved in the minimum amount of methanol, and titrated with

10% KOH in methanol to the phenolphthalein end point. The precipitated salts were filtered and the filtrate was evaporated to dryness on a rotary evaporator at 40 °C. The residue was then taken up in benzene and filtered. The solvent was removed on a rotary evaporator to give the (S)-aminimide enantiomer (3.88 g, 89%), characterized in $CDCl_3$ by ^1H-NMR spectroscopy, D_2O exchange experiments and used directly in the next step in the synthesis.

EXAMPLE 41.

Synthesis of the Chiral Aminimide.



1-(5'[3'-methyluracil]methyl)-1-methylhydrazine (18.4 g, 0.1 mol, prepared by the alkylation of 2-methylphenylhydrazone with 5-chloromethyl-3-methyluracil in ethanol, as described in 24 J. Org. Chem. 660 (1959) and references cited therein, followed by removal of the benzoyl group by acid hydrolysis) in toluene (100 mL) was cooled to 5 °C in an ice bath. A solution of *p*-isopropylphenyl-chloromethylanalide (21.1 g, 0.1 mol, prepared from

chloracetyl chloride and *p*-isopropylanaline), in toluene (100 mL), was added thereto, with vigorous stirring over a 1 hour period, maintaining a temperature of 5 °C. The reaction mixture was stirred at room temperature overnight. The solution was cooled to 0 °C, and the precipitated hydrazinium chloride salt was filtered, washed with cold toluene and dried in a vacuum oven at 40 °C/30" to yield the crude racemic product (4.77 g, 98%). This racemate was slurried in ethanol (100 mL), a slight molar excess of moist silver oxide was added, and the mixture was stirred at room temperature overnight. This racemate was resolved via its tartrate salts and isolated as the iodide using the method of Singh, above, characterized by HPLC on Crownpack™ CR(+) chiral stationary phase (Daicell Chemical Industries Ltd.) using pH 2 aqueous mobile phase. ^{1}H-NMR (DMSO-d_6): chemical shifts, peak integrations & D_2O exchange experiments were diagnostic for the desired structure.

EXAMPLE 42.

Synthesis of 3-methyl-5-chloromethyluracil

A. N-methylurea (74.08 g, 1 mol) and diethylethoxymethylenemalonate (216.2 g,1 mol) were heated together at 122 °C for 24 hours, followed by 170 °C for 12 hours, to give the 3-methyluracil-5-carboxylic acid ethyl ester in 35% yield, following recrystallization from ethyl acetate.

B. 3-methyluracil-5-carboxylic acid ethyl ester (30 g) was saponified with 10% NaOH to yield the free acid in 92% yield, after standard work-up and recrystallization from ethyl acetate.

C 3-methyluracil-5-carboxylic acid (20 g) was decarboxylated at 260 °C to give a quantitative yield of 3-methyluracil.

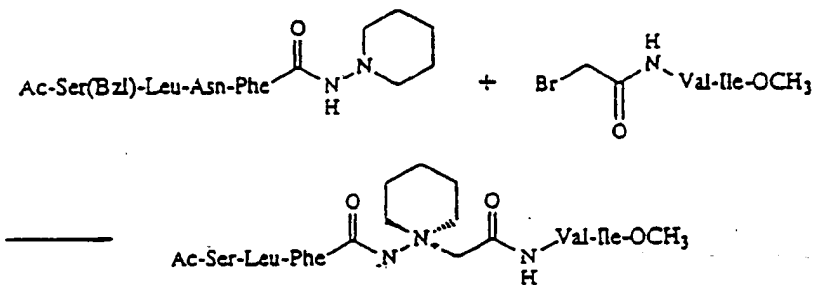
D. 3-methyluracil-5-carboxylic acid was treated with HCl and CH_2O, using standard chloromethylation conditions, to give 3-methyl-5-chloromethyluracil in 52% yield, following standard work-up and recrystallization from ethyl

acetate: mp. 186 °C; ^{1}H-NMR (DMSO-d_6): chemical shifts, peak integrations & D_2O exchange experiments were diagnostic for the desired structure.

EXAMPLE 43.

Synthesis of a peptidomimetic HIV protase inhibitor

This example teaches the synthesis of a competitive inhibitor for the HIV protease with enhanced stability, based on the in sertion of a chiral aminimide residue into the scissile bond position of the substrate Ac-L-Ser(Bzl)-L-Leu-L-Phe-L-Pro-L-Ile-L-Val-OMe (see, e.g., 33 J. Med. Chem. 1285 (1990) and references cited therein).



0.735 g (1 mmol) of Ac-Ser(Bzl)-Leu-Asn-Phe-CO-NH-NC5H10 is dissolved in the minimum amount of DMF, and 0.344 g of BrCH2CONH-Val-Ile-OMe, prepared by treatment of H2N-Val-Ile-OMe with (BrCH2CO)2O according to the method of Kent (256 Science 221 (1992), is added thereto. The mixture is heated to 60 ∞C and stirred at this temperature overnight. At this point the DMF is removed under high vacuum, and the desired (S) isomer is obtained from the enantiomeric mixture after neutralization by standard normal-phase silica chromatography to yield the protected peptide. The side chain blocking groups are then removed using standard peptide deprotection techniques to yield the product Ac-Ser-Leu-Asn-

Phe-CON-N+(C5H10)-CH2-CO-NH-Val-Ile-OMe, useful as a enhanced stability competitive inhibitor for the HIV protease.

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EXAMPLE 44.

Synthesis of the Tetrapeptide Hydrazone

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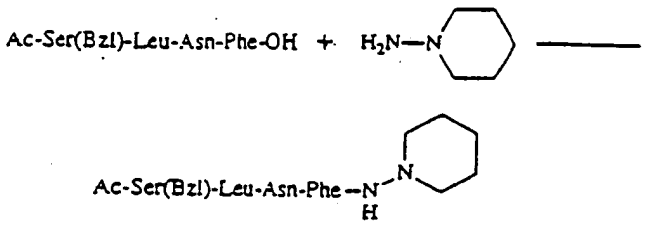

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0.653 g (1 mmol) of AcSer(Bzl)-Leu-Asn-Phe-OH, prepared via standard peptide synthesis techniques (see 33 J. Med. Chem. 1285 (1990) and references cited therein), is coupled with 0.10 g (1 mmol) of 1-aminopiperidine using standard peptide-coupling methods and chemistries (see 33 J. Org. Chem. 851 (1968)) to give a 97% yield of the hydrazide, isolated by removal of the reaction solvent in vacuo.

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EXAMPLE 45

Synthesis of a chiral monomer useful in polymerizations yielding crosslinked polymer chains

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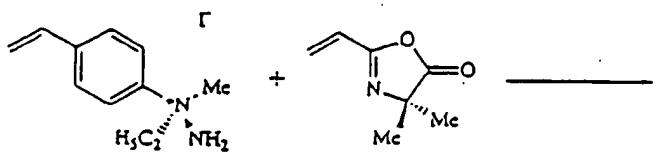

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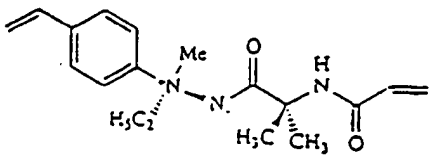
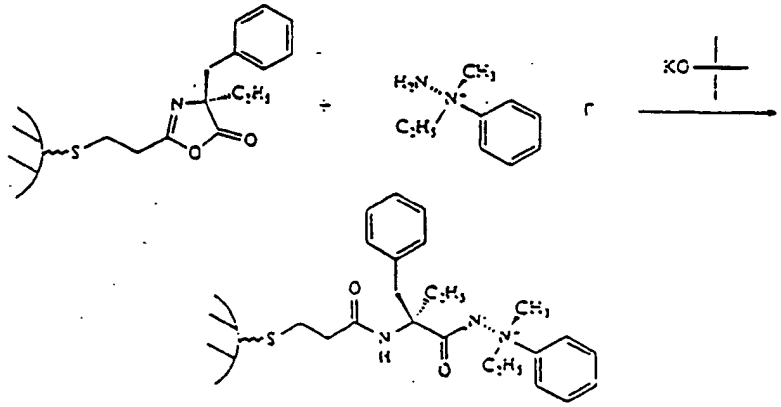


3.18 g (0.01 mol) of (S)-1-methyl-1-ethyl-1-p-vinyl- benzylhydrazinium iodide, prepared from p-vinylbenzyl chloride and 1-methyl-1-ethylhydrazine using standard alkylation conditions, and isolated as the (S)-enantiomer by the method of Singh (103 J. Chem. Soc. 604 (1913)), are added to 75 ml of anhydrous t-butanol. The mixture is stirred under nitrogen and 1.12 g (0.01 mol) of potassium t-butoxide was added. The mixture is stirred for 24 hours at room temperature and the reaction mixture is diluted with 75 ml of anhydrous THF, cooled in an ice bath and 1.39 g (0.01 mol) of 2-vinyl-4,4-dimethylazlactone in 50 ml of THF are then added over a 15-min. period. When addition is complete, the mixture is allowed to warm to room temperature and stirred at room temperature for 6 hours. The solvent is stripped under aspirator vacuum on a rotary evaporator to yield 3.0 g (92%) of crude monomer. The product is recrystallized from ethyl acetone at -30^{0}C to yield pure crystalline momomer, useful for fabricating crosslinked chiral gels, beads, membranes and composites for chiral separations, particularly for operation at high pH. NMR (CDCl3) chemical shifts, presence of vinyl groups in 6 ppm region, vinyl splitting patterns, peak integrations and D2O experiments diagnostic for structure. FTIR absence of azlactone CO band in 1820 cm-1 region.

EXAMPLE 46.

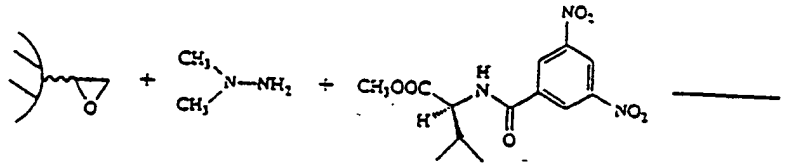
Functionalization of silica with an oxazolone followed by conversion to a chiral aminimide useful in the resolution of racemic carboxylic acids

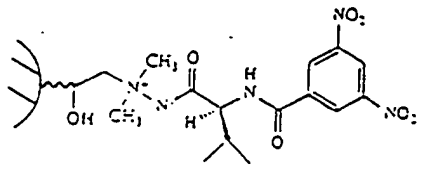


2.81 g (0.01 mol) of (S)-1-methyl-1-ethyl-1-phenyl- hydrazinium iodide, prepared by the method of Singh (103 J. Chem Soc. 604 (1913)), is added to 100 ml anhydrous t-butanol. The mixture is stirred under nitrogen and 1.12 g (0.01 mol) potassium t-butoxide was added. The mixture is stirred for 24 hours at room temperature, after which the reaction mixture is diluted with 100 ml anhydrous THF. To this mixture is added 5.0 g silica functionalized with the Michael-addition product of (S)-4-ethyl-4-benzyl-2-vinyl- 5-oxazolone to mercaptopropyl-functional silica. This mixture is stirred at room temperature for 8 hours. The functionalized silica is collected by filtration and successively reslurried and refiltered using 100-ml portions of toluene (twice), methanol (four times) and water (twice). The resulting wet cake is dried in a vacuum oven at 60 ∞C under 30" vacuum to constant weight, yielding 4.98 g of chiral-aminimide-functionalized silica, useful for the separation of racemic mixtures of carboxylic acids, such as ibuprofen, ketoprofen and the like.

EXAMPLE 47.

Functionalization of silica with a chiral aminimide for use in the separation of mandelates





10.0 g epoxy silica (15 micron Exsil C-200 silica) is slurried in 75 ml methanol and shaken to uniformly wet the surface. To this slurry is added 6.01 g (0.01 mol) 1,1-dimethylhydrazine, and the mixture is allowed to stand at

room temperature with periodic shaking for 45 min. 32.5 g (0.1 mol) of (S)-3,5-dinitrobenzoylvaline methyl ester is added and the mixture is allowed to stand at room temperature with periodic shaking for three days. The functionalized silica is then collected by filtration, re-slurried in 100 ml methanol and re-filtered a total of five times, then dried in a vacuum oven at 60 ∞C/30" overnight to give 9.68 g of the product. This functionalized silica is slurry packed from methanol into a 0.46 x 15 cm stainless steel column and used to separate mixtures of mandelic acid derivatives under standard conditions.

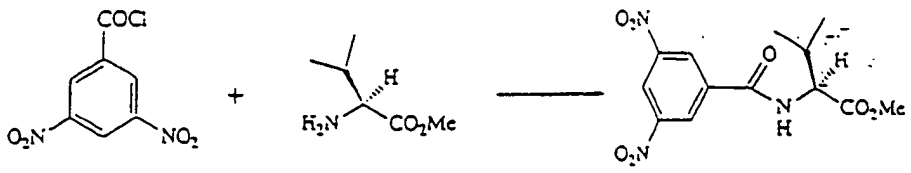
EXAMPLE 48.

Preparation of epoxy silica

50 g of 5 micron C-200 Exsil silica (SA 250 M2/g) is added to 650 ml toluene in a two-liter three-necked round-bottomed flask equipped with a Teflon paddle stirrer, a thermometer and a vertical condenser set up with a Dean-Stark trap through a claisen adaptor. The slurry is stirred, heated to a bath temperature of 140 ∞C and the water is azeotropically removed by distillation and collection in the Dean-Stark trap. The loss in toluene volume is measured and compensated for by the addition of incremental dry toluene. 200 g of glycidoxypropyl trimethoxysilane is added carefully through a funnel and the mixture is stirred and refluxed overnight with the bath temperature set at 140 ∞C. The reaction mixture is then cooled to about 40 ∞C. The resulting functionalized silica is collected on a Buechner filter, washed twice with 50 ml toluene, sucked dry, reslurried in 500 ml toluene, refiltered, reslurried in 500 ml methanol and refiltered a total of four times. The resulting methanol wet cake is dried overnight in a vacuum oven set for 30" at 60 ∞C to yield 48.5 g of epoxy silica.

EXAMPLE 49

Synthesis of N-3,5-Dinitrobenzoyl-(S)-Valine Methyl Ester



13.12 g (0.1 mol) of (S)-valine methyl ester is added with stirring to a solution of 8 g (0.2 mol) sodium hydroxide in 50 ml of water, cooled to about 10 ∞C, and the mixture is stirred at this temperature until complete solubilization is achieved. 23.1 g (0.1 mol) of 3,5-dinitrobenzoylchloride is then added dropwise with stirring, keeping the temperature at 10-15 ∞C with external cooling. After the addition was complete, stirring is continued for 30 min. To this solution is added over a 10-min. period 10.3 ml (1.25 mol) of concentrated hydrochloric acid, again keeping the temperature at 15 ∞C. After this addition is complete, the reaction mixture is stirred for an additional 30 min. and cooled to 0 ∞C. The solid product is collected by filtration, washed well with ice water and pressed firmly with a rubber dam. The resulting wet cake is recrystallized from ethanol/water and dried in a vacuum oven under 30" vacuum at 60 ∞C to yield 28.5 g (90%) of N-3,5-dinitrobenzoyl-(S)-valine methyl ester. NMR (CDCl3): chemical shifts, splitting patterns, integrations and D2O exchange experiments diagnostic for structure.

EXAMPLE 50.

Preparation of aminimide-containing ion-exchange silica matrix

This example describes preparation of an aminimide-functionalized ion-exchange silica matrix using epoxy silica as the support to be modified. The reaction sequence is:

Epoxy Silica + (CH3)2NNH2 + Et2NCH2CH2COOEt --->

-Si-O-SiCH2CH2CH2OCH2CH(OH)CH2N(CH3)2NCOCH2CH2NEt2

25 g of epoxy silica (15micron Exsil AWP 300 silica, with surface area of 100 m2/g) is slurried in 100 ml methanol until completely wetted by the solvent. 10.2 g of 1,1-dimethylhydrazine are then added with swirling and the mixture allowed to stand at room temperature for 3 hours. 24.7 g of Et2NCH2CH2COOEt are then added and the mixture kept at room temperature with periodic shaking for 2 days.

The diethylaminoethyl (DEAE) functionalized silica is collected by filtration, re-slurried in 100 ml methanol and re-filtered a total of five times. The packing is dried in a vacuum oven at 60_C/30" overnight. A 1.0 ml bed of this material is then packed in a 15 mM NaAc buffer at pH 7.7. The column is then equilibrated with 15 mM NaAc buffer at pH 5.6, and a solution of 1 mg/ml ovalbumin in this buffer run through the bed at a flow rate of 1.6 ml/min. A total of 59.2 ml of protein solution is run.

The column is then washed with 41.7 ml of 15 mM NaAc buffer at pH 5.58 and at a flow rate of 3.9 ml/min. The bound protein is eluted using 23.4 ml of 0.5M NaCl at a flow rate of 3.9 ml/min. The eluent (15.2 ml) is then collected and the transmission of an aliquot measured at 280 mμ with a spectrophotometer. The ovalbumin concentration is determined from a calibration curve.

EXAMPLE 51.

Preparation of aminimide-containing size-exclusion silica matrix

This example describes preparation of an aminimide-functionalized size-exclusion silica matrix using the epoxy silica support described in Example _.

10.0 g of epoxy silica (15micron Exsil C-200 silica, with surface area of 250 m2/g) is slurried in 75 ml of methanol

and shaken to uniformly wet the surface. To this slurry is added 10.2 g of 1,1-dimethylhydrazine. The mixture is allowed to stand at room temperature with periodic shaking for 45 min.

15 g of ethyl acetate are then added and the mixture allowed to stand at room temperature with periodic shaking for 3 days. The functionalized silica is then collected by filtration, re-slurried in 100 ml methanol, re-filtered a total of five times and dried in a vacuum oven at 60 ∞C/30" overnight. The functionalized silica is slurry packed from methanol into a 10 mm interior-diameter jacketed glass column with adjustable pistons to provide an 8 cm-long packed bed. This packing is used to separate mixtures of polyethylene glycol polymers of varying molecular weight with good resolution using a mobile phase.

In a second experiment, the bulk packing was found to selectively adsorb polyethylene-glycol functionalized hemoglobin from serum samples taken from test animals that had been treated with this derivative as a blood substitute. Filtration of the serum, after treatment with the bulk packing, gave a serum free from the functionalized hemoglobin, thus allowing blood screening or testing by means of standard methods.

EXAMPLE 52.

Preparation of aminimide-functional PVA bead for selectively binding polyethylene glycol containing species (intelligent macromolecule) .

This example describes preparation of an aminimide-functionalized crosslinked PVA matrix.

5.0 g of VA-epoxy beads(Riedel-de-Haeen crosslinked PVA with 300umol of epoxy equivalents /g. is slurried in 50 ml of methanol and shaken to uniformly wet the surface. To this slurry is added 7.65 g of 1,1-dimethylhydrazine. The mixture is allowed to stand at room temperature with periodic shaking for 45 min.

11.25 g of methyl acetate is then added and the mixture allowed to stand at room temperature with periodic shaking for 3 days. The functionalized resin is then collected by filtration, re-slurried in 100 ml methanol, re-filtered a total of five times and dried in a vacuum oven at 60 C/30" overnight. The bulk packing is used to selectively adsorb polyethylene-glycol functionalized hemoglobin from serum samples taken from test animals that had been treated with this derivative as a blood substitute. Filtration of the serum, after treatment with the bulk packing, gave a serum free from the functionalized hemoglobin, thus allowing blood screening or testing by means of standard methods.

EXAMPLE 53.

Preparation of aminimide-functional PVA bead for selectively binding polyethylene glycol containing species (intelligent macromolecule)

This example describes preparation of a second type of aminimide-functionalized crosslinked PVA matrix.

5.0 g of VA-epoxy beads(Riedel-de-Haeen crosslinked PVA with 300umol of epoxy equivalents/g is slurried in 50 ml of methanol and shaken to uniformly wet the surface. To this slurry was added 7.65 g of 1,1-dimethyl-hydrazine. The mixture is allowed to stand at room temperature with periodic shaking for 45 min.

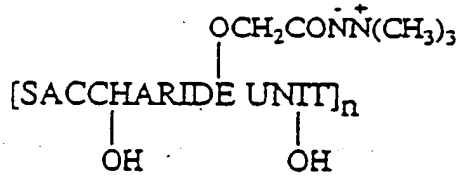
20.0 g of methyl caproate are then added and the mixture allowed to stand at room temperature with periodic shaking for 3 days. The functionalized resin is then collected by filtration, re-slurried in 100 ml methanol, re-filtered a total of five times and dried in a vacuum oven at 60^{0}C/30" overnight. The bulk packing is used to selectively adsorb polyethylene-glycol functionalized hemoglobin from serum samples taken from test animals that had been treated with this derivative as a blood substitute. Filtration of the serum, after treatment with the bulk packing, gave a serum free from

the functionalized hemoglobin, thus allowing blood screening or testing by means of standard methods.

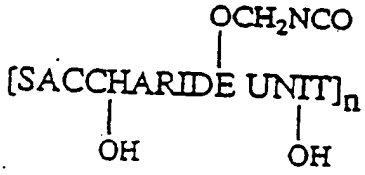
EXAMPLE 54.

Coating of a silica matrix with hydroxypropylcellulose functionalized with an aminimide

Hydroxypropylcellulose is mono-functionalized by reaction, under strong alkaline conditions (preferably provided by a strong base, such as potassium t-butoxide) with ClCH2CON-N+(CH3)3. The result is replacement of approximately one hydroxyl group in each saccharide unit with the aminimide as follows:



The resulting aminimide derivative is coated onto a surface (e.g., silica). Upon heating to 140 ∞C, the N(CH3)3 group leaves, resulting in formation of an isocyanate moiety:



The isocyanate groups then react with unreacted hydroxyl groups on the saccharide units to produce a cross-linked coating.

Alternatively, the cellulose can be coated onto the surface and immobilized using standard techniques (e.g., reaction with bisoxiranes), and then mono, di- or tri-

substituted with desired aminimide derivatives as described above.

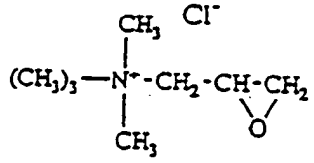
The foregoing reaction sequence can also be employed with polymers or oligomers bearing NH or SH groups instead of hydroxyl groups and can also be utilized to fabricate structures such as crosslinked cellulose membranes.

EXAMPLE 55.

Coating of a silica matrix via polymerization of an aminimide on the matrix

This example illustrates an alternative immobilization technique, namely, polymerizing aminimide precursors containing vinyl groups and which have been coated onto a surface. The chemistry resembles the approach described above, except polymerization forms a sturdy shell around an existing support rather than creating a solid block of material.

This sequence makes use of the reaction described above. An epoxide,



is combined with methyl methacrylate and dimethylhydrazine as set forth in 2.a above to form CH=C(CH3)-CO-NN(CH3)2-CH2-CH(OH)-CH2-N+(CH3)3Cl-. 3.11 g of this material and 0.598 g n-methylol acrylamide are dissolved in 75 ml of methanol, and 3.54 ml of water is then added. To this solution is added 15 g of epoxy silica (15u Exsil AWP 300 silica. with surface area of 100 m2/g).

The mixture is stirred in a rotary at room temperature for 15 min and then stripped using a bath temperature of 44°C to a volatiles content of 15% as measured

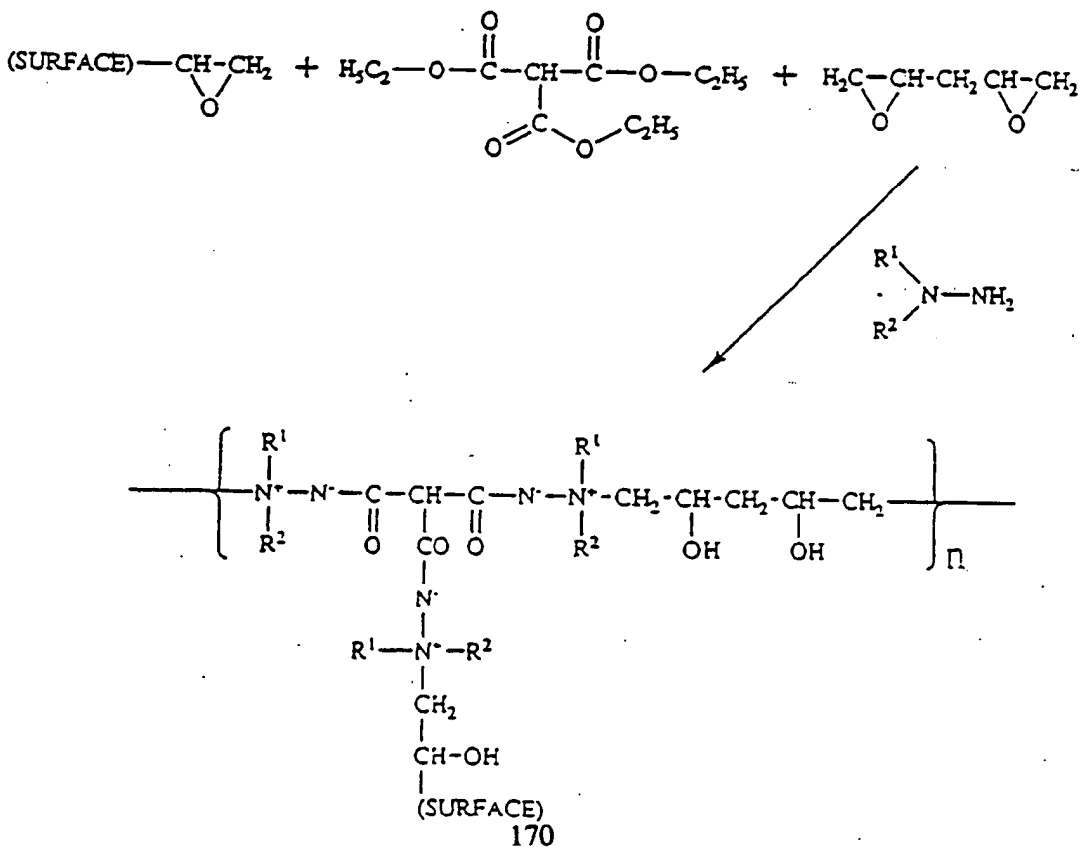
by weight loss (from 25-200^{0}C with a sun gun). The coated silica is slurried in 100 ml of isooctane containing 86 mg of VAZO-64 dissolved in 1.5 ml toluene which had been de-aerated with nitrogen. The slurry is thoroughly de-aerated wtih nitrogen and then stirred at 70^{0}C for two hours.

The coated silica is collected by filtration and washed three times in 100 ml methanol and air dried. The silica is heated at 120^{0}C for 2 hours to cure the coating. 13.1 g of coated silica are obtained. A 1 ml bed of this material is packed in an adjustable glass column and successfully used to separate BSA from lactoglobulin.

EXAMPLE 56.

Preparation of a silica support containing crosslinked aminimide polymer chains

In this example, an epoxy-functionalized surface is reacted with disubstituted hydrazine, a bisepoxide and a triester to form a crosslinked network of aminimide chains attached covalently to the surface as follows:



The reaction can be carried out in water at room temperature without special conditions.

EXAMPLE 57.

Preparation of cross-linked porous aminimide ion-exchange beads

This example describes preparation of three-dimensional cross-linked porous copolymeric aminimide ion-exchange beads. It involves reaction of three monomers:

Monomer A: CH2=CH-CON-N+(CH3)3

Monomer B: CH2=C(CH3)-CON-N+(CH3)2-CH2-CH(OH)-CH2-N+(CH3)3Cl-

Crosslinker: CH2=CH-CO-NH-C(CH3)2-CON-N+(CH3)2-CH2-Ph-CH=CH2

where Ph is phenyl.

Preparation of Monomer A: This monomer was prepared according to the method described in 21 J. Polymer Sci., Polymer Chem. Ed. 1159 (1983).

Preparation of Monomer B: 30.3 g (0.2 mol) of glycidyl-trimethylammonium chloride is dissolved in 100 ml of methanol and filtered free of insolubles. 22 g (0.22 mol) of methyl methacrylate is added thereto, followed by 12 g (0.2 mol) of 1,1-dimethylhydrazine. The solution grew warm and turned slightly pink. It is allowed to stand for 6 days at room temperature, and is then treated with charcoal, filtered, and concentrated on a rotary evaporator at 55^{0}C and 10mm to produce a thick lavendar-colored, viscous material. This material is triturated with diethylether and hot benzene and dissolved in the minimum amount of methanol. The mixture is then treated with charcoal, filtered, heated to boiling and brought to the cloud point with ethyl acetate. The resulting solution is allowed to stand at 0^{0}C for a week. The white crystals that formed are collected by filtration, washed with cold ethyl acetate and dried in a vacuum oven at room temperature to yield 7.3 g of monomer B.

Preparation of Monomer C: 18 g (0.3 mol) of 1,1-dimethylhydrazine is dissolved in 50 ml CH2Cl2 and cooled in an ice bath with stirring. 41.7 g (0.3 mol) of vinylazlactone in 50 ml CH2Cl2 are added slowly to keep the temperature below 5 ∞C. The clear solution is stirred and allowed to come to room temperature over 1 hour (resulting in formation of a white solid) and is stirred at room temperature for an additional 1.5 hours. The white solid is collected by filtration, re-slurried in 100 ml CH2Cl2 and re-filtered. It is then dried in a vacuum oven at room temperature overnight to yield a total of 26.81 g of the intermediate CH2=CH-CO-NH-C(CH3)2-CO-NH-N-(CH3)2. 10.0 g (0.05 mol) of this intermediate and 7.66 g (0.05 mol) of vinyl benzyl chloride are dissolved in a mixture of 50 ml ethanol and 50 ml CH3CN. The solution is refluxed for 4 hours under a nitrogen stream. It is then cooled to room temperature and concentrated on a rotary evaporator at 55 ∞C to produce a thick yellow oil. The oil is triturated three times with diethylether to yield 17.08 g of an off-white solid. This solid is dissolved in 100 ml of hot methanol and filtered through a celite pad to remove a small amount of gelatinous material, and the clear filtrate is stripped to yield 10.0 g of Monomer C as a white solid.

Polymerization: 1 ml of the emulsifier Span 80 and 175 ml of mineral oil are introduced into a 500 ml round-bottomed flask equipped with stirrer and a heating bath. The mixture is mechanically stirred at 70 RPM and brought to a temperature of 55 °C. 40.5 g of monomer A, 7.2 g of monomer B and 5.7 g of the cross-linker are dissolved in 100 ml of demineralized water and heated to 55°C To this solution is added 150 mg of ammonium persulfate, and the mixture is then poured into the stirred mineral oil. The agitation is adjusted to produce a stable emulsion with an average droplet diameter of approximately 75u (as determined with an optical microscope).

After 15 min, 0.15 ml of TMED is added and stirring is continued for an additional 45 min. The reaction mixture is

cooled and allowed to stand overnight. The supernatant mineral oil phase is removed by aspiration and the beads are collected by decantation. The beads are washed three times with a 0.05% solution of Triton X-100 in demineralized water to remove any remaining mineral oil and then washed with water and allowed to settle. The water is removed by decantation.

This procedure is repeated a total of five times. The beads obtained at the conclusion of the foregoing steps had a mean diameter of approximately 75 u and an ion-exchange capacity of 175 ueq/ml.

EXAMPLE 58.

Preparation of an aminimide-based electrophoretic gel

This example describes preparation of an aminimide electrophoresis gel. As a control, the standard Sigma protein electrophoresis mix (available from Sigma Chemical Co., St. Louis, MO) is run on an acrylamide/methylene bisacrylamide linear gradient gel prepared using a gradient maker with 5% and 12.5% monomer solutions, as shown below. The gel is overlayed with isobutanol and allowed to polymerize overnight.

Monomer	5% Monomer	12.5%
Lower Tris	5.0 ml	5.0 ml
H2O	11.7 ml	4.7 ml
30% Acrylamide	3.3 ml	8.3 ml
Glycerol	---	2.0 ml
Ammonium Persulfate	30 ul	30 ul
TMED	15 ul	15 ul

Lower Tris 1.5M: 6.06 g Tris base, 8 ml 10% SDS, volume adjusted to 90 ml with double-distilled water. The pH

is adjusted to 6.0 with concentrated HCl, and the final volume adjusted to 100 ml with DD water.

Acrylamide 30% w/v: 29.2 g acrylamide, 0.8 g of methylene bisacrylamide and 100 ml DD water.

SDS 10% w/v: 10 g of SDS is dissolved in DD water and adjusted to a volume of 100 ml.

Ammonium persulfate 10%: 0.1 g ammonium persulfate is dissolved in 0.9 ml DD water. The solution is used within 4 hours of preparation.

TMED: used directly as obtained from Sigma Chemical Co., St. Louis, MO, under the tradename TMEDA.

A second gel is prepared by replacing the acrylamide with an equal weight of the aminimide monomer CH2=CH-CO-N-N(CH3)3 and the protein standard is run in the same way as the first.

Separation of proteins with the aminimide gel is equivalent to the acrylamide gel, but the aminimide gel produced Rf (i.e., the ratio of distance traversed by a particular protein to the distance traversed by the solvent front) levels approximately 20% higher than those of the acrylamide gel.

EXAMPLE 59.

Preparation of aminimide-based latex particles

591.1 ml of distilled water is charged to a three-necked round-bottomed flask. A nitrogen dip tube is placed below the liquid level and the nitrogen flow rate set to 2 cm3/min. The solution is mechanically agitated with a Teflon paddle at 250 RPM and heated to 80°C over a half-hour period. In a separate flask is dissolved 121.6 g of butyl acrylate, 54.6 g of ethyl acrylate, 13.0 g of acrylic acid, 9.97 g of methyl methacrylate, 59.7 g of the aminimide monomer CH2=CH-CO-N-N(CH3)2-CH2-CH2-OH and 0.92 g of Aerosol TR-70 so as to obtain solution without exceeding a temperature of 25°C. When completely dissolved, 1.53 g of additional TR-70 is added and the mixture is then stirred until solution is achieved.

20.7 ml of distilled water is purged with nitrogen for 10 min and 1.59 g of K2S2O8 is dissolved in it. This persulfate solution is added to the heated water in the reaction flask after it stabilized at 80°C. The nitrogen dip tube is raised and a nitrogen blanket is maintained. The monomer mix is pumped in at a steady, calibrated rate such that the constant addition took exactly 4 hours. When addition is complete, the latex was post-heated at 80°C for 1 hour, cooled to 25°C and titrated to pH 5.0 by dropwise addition of triethylamine (approximately 20 cm3) over 20 min with agitation. The latex is then filtered through cheese cloth and stored. Average particle size is measured at about 0.14u.

EXAMPLE 60.

Incorporation of an aminopyridinium functionality into an amininmide backbone

A solution of 1-amino-4-pyridiniumcarboxylic *tert*-butyl ester iodide (3.22 g, 10 mmol) in THF (25 ml) is added to a solution of N-benzoyl-N'-acetic acid-N'isobutyl-N'-methylhydrazinium inner salt (2.64 g, 10 mmol) and dicyclohexylcarbodiimide (2.06 g, 10 mmol) in THF (100 ml) and stirred for two hours at room temperature. The suspension is treated with Amberlite IR-45 (or an equivalent basic resin) for three hours at room temperature then filtered to remove both the resin and precipitated dicyclohexyl urea. The filtrate is concentrated and the residue is recrystallized from ethyl acetate to afford the bis hydrazinium inner salt (3.56 g, 78%).

The entirety of this material is dissolved in acetonitrile (150 ml). Amberlite IR-118 is added and the mixture is heated at reflux to exhaustion of the ester. The resin is removed by filtration and the solution is treated with dicyclohexylurea (1.61 g, 7.8 mmol) in acetonitrile (25 ml). After three minutes of stirring, 1-benzyl-1-methylhydrazine (1.38 g, 9.36 mmol) is added neat, and the resultant suspension

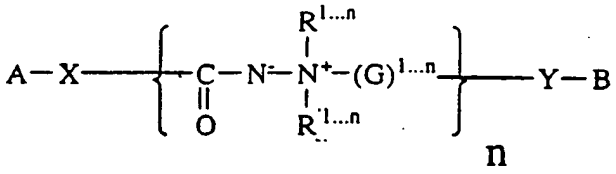
is stirred at room temperature for two hours. Removal of the precipitated dicyclohexyl urea by filtration and concentration of the filtrate affords a solid (5.01 g), which is not isolated, but dissolved in isopropyl alcohol (100 ml) and propylene oxide (0.542 g, 9.36 mmol) is added. The mixture is heated at reflux for seven hours and the volatile components are then removed in vacuo. Crystallization of the residue from ethyl acetate provides the tris-ylide (2.95 g, 5.30 mmol, 68%).

It should be apparent to those skilled in the art that other aminimide compounds and compositions and other processes for preparing said compounds and compositions not specifically disclosed in the instant specification are, nevertheless, contemplated thereby. Such other compositions and processes are considered to be within the scope and spirit of the present invention. Hence, the invention should not be limited by the description of the specific embodiments dislosed herein.

THE CLAIMS

What is claimed is:

1. A composition having the structure:



wherein

a. A and B are the same or different, and each is selected from the group consisting of a chemical bond; hydrogen; and electrophilic group; a nucleophilic group; R; R'; an amino acid derivative; a nucleotide derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; and a macromolecular component, wherein A and B are optionally connected to each other or to other structures and R and R' are as defined below;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n \geq 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

2. The composition of claim 1 wherein $n > 2$.

3. The composition of claim 1 wherein at least one of R and R' includes a hydroxyl containing substituent.

4. The composition of claim 1 wherein at G includes at least one of an aromatic ring, a heterocyclic ring, a carbocyclic moiety, an alkyl group or a substituted derivative thereof.

5. The composition of claim 1 wherein A and B are the same.

6. The composition of claim 1 where R and R' are different so that the composition is chiral.

7. The composition of claim 1 wherein at least one of A and B is a terminal-structure moiety of formula T-U, wherein;

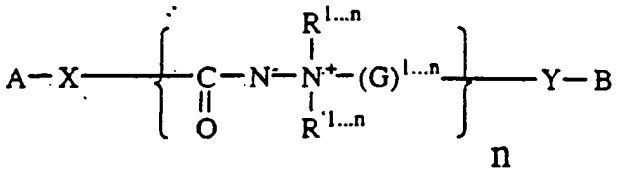
a. U is selected from the group consisting of aliphatic chains having from 2 to 6 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted cycoalkyl, and substituted or unsubstituted heterocyclic rings; and

b. T is selected from the group consisting of -OH, $-NH_2$, -SH, $(CH_3)_3N^+$-, SO_3-, $-COO^-$, CH_3, H and phenyl.

8. The composition of claim 1 wherein at least one of A and B is $HO\text{-}CH_2\text{-}(CHOH)_n\text{-}$.

9. The composition of claim 1 wherein A and B are part of the same cyclic moeity.

10. A peptide mimetic having the structure



wherein:

a. A and B are the same or different, and at least one is an amino acid derivative of the form $(AA)_m$, wherein AA is a natural or synthetic amino acid residue and m is an integer, and A and B are optionally connectec to each other or to other structures;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

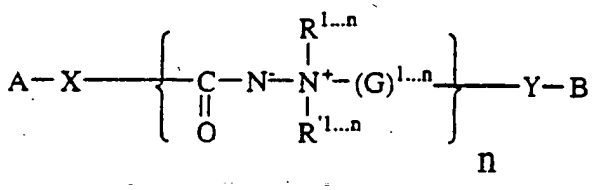
c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

d. G is a chemical bond or connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n \geq 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

11. A nucleotide mimetic having the structure:



wherein:

a. A and B are the same or different, and at least one is a nucleotide derivative, wherein A and B are optionally connected to each other or to other structures;

b. X and Y are the same or different and each rerprsents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units

and have a selected stereochemical arrangement about the carbon atom to which they are attached;

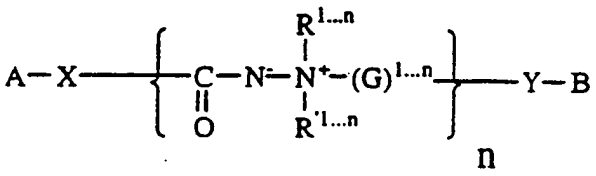
d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n \geq 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

12. The nucleotide mimetic of claim 11 wherein A is a nucleotide derivate of the form $(NUCL)_1$, wherein 1 is an integer, such that $(NUCL)_1$, is a natural or synthetic nucleotides when 1=1, a nucleotide probes when 1=2-25 and an oligonucleotides when 1>25 including both deoxyribose (DNA) and ribose (RNA) variants.

13. A carbohydrate mimetic having the structure:



wherein:

a. A and B are the same or different, and at least one is a carbohydrate derivative; wherein A and B are optionally connected to each other or to other structures;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

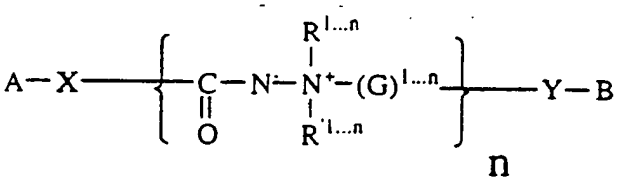
d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n > 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

14. The carbohydrate mimetic of claim 13 wherein A and B each is a natural carbohydrate, a synthetic carbohydrate residue or derivative thereof or a related organic acid thereof.

15. A pharmaceutical compound having the structure:



wherein:

a. A and B are the same or different, and at least one is an organic structural motif; wherein A and B are optionally connected to each other or to other structures;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

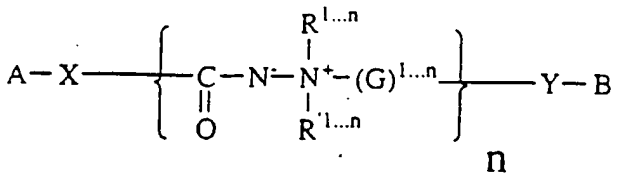
d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n > 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

16. The pharmaceutical compound of claim 15 wherein the structural motif of the organic compound mimics or complements the structure of a pharmaceutical compound or a pharmacophore or metabolite thereof and has specific binding properties to ligands.

17. A reporter compound having the structure:



wherein:

a. A and B are the same or different, and at least one is a reporter element; wherein A and B are optionally connected to each other or to other structures:

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

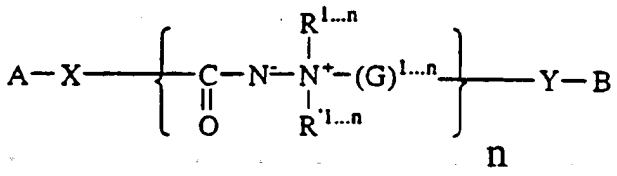
e. $n > 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

18. The reporter compound of claim 17 wherein the reporter element is a natural or synthetic dye or a photographically active residue which possesses at least one reactive group which may be synthetically incorporated into the aminimide structure or reaction scheme and may be attached through the groups without adversely interfering with the reporting functionality of the group.

19. The reporter compound of claim 17 wherein the reactive group is amino, thio, hydroxy, carboxylic acid, acid chloride, isocyanate alkyl halide, aryl halide or an oxirane group.

20. A polymer having the structure:



wherein:

a. A and B are the same or different, and at least one is an organic moiety containing a polymerizable group; wherein A and B are optionally connected to each other or to other structures;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives

thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

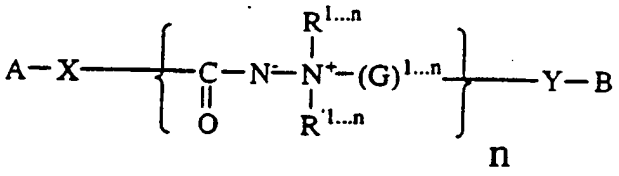
d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n > 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

21. The polymer of claim 20 wherein the polymerizable group of the organic moiety is a vinyl group, oxirane group, carboxylic acid, acid chloride, ester, amide, lactone or lactam.

22. A substrate having the structure:



wherein:

a. A and B are the same or different, and at least one is a macromolecular component, wherein A and B are optionally connected to each other or to other structures;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n > 1$;

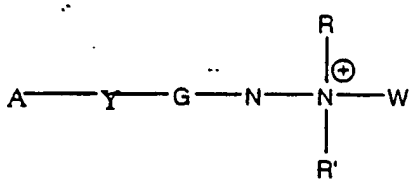
provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R.

23. The substrate of claim 21 wherein the macromolecular component is a surface or structures which is attached to the aminimide module via a reactive group in a manner where the binding of the attached species to a ligan-receptor molecule is not adversely affected and the interactive activity of the attached functionality is determined or limited by the macromolecule.

24. The substrate of claim 23 wherein the macromolecule component has a molecular weight of at least about 1000 Daltons.

25. The substrate of claim 24 wherein the molecular component is in the form of an ceramic particle, a nonoparticle, a latex particle, porous or non-porous beads, a membrane, a gel, a macroscopic surface or a functionalized or coated version or composite thereof.

26. A chiral composition of matter having the structure



wherein

a. A is a chemical bond; hydrogen; an electrophilic group; a nucleophilic group; R'; an amino acid derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component, wherein R is as defined below;

b. Y represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. W is -H or $-H_2$ X where X is an anion;

d. R and R' are the same or different and each is an alkyl, cycloalkyl, aryl, aralkyl or alkaryl group or a substituted or heterocyclic derivative thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon a to which they are attached; and

e. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the

quaternary nitrogen; provided that if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen.

27. The composition of claim 26 wherein X is a halogen or tosyl anion.

28. The composition of claim 26 wherein A is a terminal-structural moiety of formula T-U, wherein:

a. U is selected from the group consisting of aliphatic chains having from 2 to 6 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted heterocyclic rings; and

b. T is selected from the group consisting of -OH, $-NH_2$, -SH, $(CH_3)_3N^+$-, $-SO_3$-, $-COO^-$, CH_3, H and phenyl.

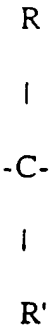
29. The composition of claim 27 wherein A is $HO-CH_2-(CHOH)_n-$.

30. The composition of claim 26 where R and R' are different so that the composition is chiral.

31. The composition of claim 26 wherein Y is a chemical bond, G is

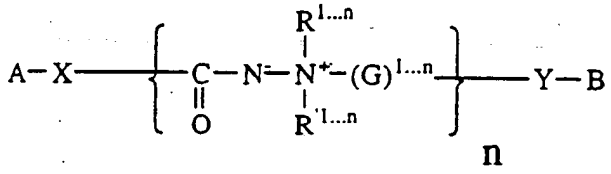
and A is $-COO^-$ or -COOR and W is $-H^-$, where R and R' differ from each other and are as described above.

32. The composition of claim 26 wherein Y is a chemical bond, G is



and A is $-COO^-$ or -COOR and W is $-H_2X$, where R and R' differ from each other and are as described above.

33. A process of synthesizing a chiral composition having the structure



wherein

a. A is a chemical bond; hydrogen; an electrophilic group; a nucleophilic group; R'; an amino acid derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component, wherein A and B are optionally connected to each other or to other structures and R is as defined below;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n > 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R;

wherein the process comprises the steps of:

acylating an asymmetric hydrazinium salt with a molecule capable of functioning both as an acylating and as an alkylating agent to form an aminimide;

reacting the aminimide with an asymmetrically disubstituted hydrazine to form a diastereomeric mixture of aminimide-hydrazinium salts.

34. The process of claim 33 which further comprises:

resolving the diastereomeric mixture and isolating a selected diastereomer;

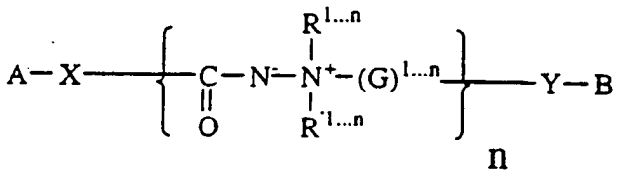
acylating the diastereomer with a second molecule capable of functioning both as an acylating and as an alkylating agent to form an aminimide;

capping the resulting aminimide; and

repeating the preceding steps at least once, if necessary, to form the desired structure.

35. The process of claim 33 wherein the asymmetric hydrazinium salt is bound to a support surface.

36. A process of synthesizing a chiral composition having the structure



wherein

a. A is a chemical bond; hydrogen; an electrophilic group; a nucleophilic group; R'; an amino acid derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component, wherein A and B are optionally connected to each other or to other structures and R is as defined below;

b. X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

c. R and R' are the same or different and each is selected from the group consisting of A, B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic, aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

d. G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

e. $n > 1$;

provided that, (1) if G is a chemical bond, Y includes a terminal carbon atom for attachment to the quaternary nitrogen; and (2) if n is 1, X and Y are chemical bonds and R and R' are the same, A and B are different and one is other than H or R;

wherein the process comprises the steps of:

alkylating an asymmetrically disubstituted acyl hydrazide with a molecule capable of functioning both as an acylating and as an alkylating agent to form a racemic mixture of aminimide isomers; and

reacting the racemic mixture with an asymmetrically disubstituted hydrazine to form a racemic mixture of aminimide-acyl hydrazide isomers.

37. The process of claim 36 which further comprises:

resolving the mixture of aminimide-acyl hydrazide isomers to isolate a desired isomer;

reacting the isolated isomer with a monofunctional alkylating agent to produce an aminimide; and

capping the aminimide.

38. The process of claim 36 which further comprises:

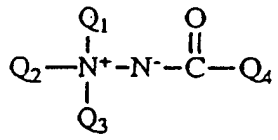
reacting the mixture of aminimide-cayl hydrazide isomers with a second molecule capable of functioning both as an acylating and as an alkylating agent to form a racemic mixture of aminimide isomers;

repeating the preceding steps at least once, if necessary, to form the desired structure.

39. The process of claim 36 wherein the asymmetrically disubstituted acyl hydrazide is bound to a support sufrace.

40. A composition prepared according to the process of any one of claim 33 to 39.

41. A lipid mimetic composition having the structure:

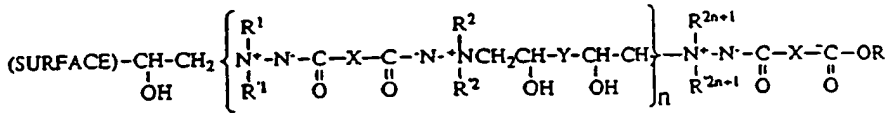


wherein Q is a chemical bond; hydrogen; an electrophilic group; a nucleophilic group; R; an amino acid derivative; a nucleotide derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; a macromolecular

component: or the substituent X(T) or $X(T)_2$; wherein R is an alkyl, cycloalkyl, aryl, aralkyl or alkaryl group or a substituted or heterocyclic derivative thereof, and T is a linear or branched hydrocarbon having between 12 and 20 carbon atoms some of which are optionally substituted with oxygen, nitrogen or sulfur ato or by an aromatic ring; and provided that at least two T substituents are present in the structure of the composition.

42. The composition of claim 41 wherein at least one Q is attached to the *a*-carbon of a naturally occurring amino acid, or at least one Q is a carbohydrate.

43. A functionalized polymer having the structure



wherein

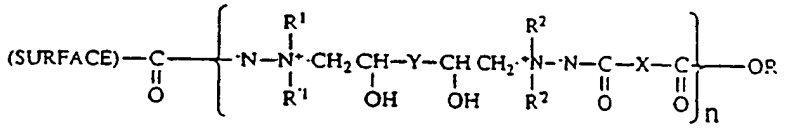
a. X and Y are connecting groups;

b. R^n and R^{1n} (where n = an integer) each represent hydrogen, alkyl, cycloalkyl, aryl, aralkyl and alkaryl;

c. (Surface) is a macromolecular component; and

d. $n \geq 1$.

44. A functionalized polymer having the formula:



wherein

a. X and Y are connecting groups;

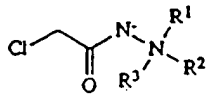
b. R^n and R^{1n} (where n = an integer) each represent alkyl, cycloalkyl, aryl, aralkyl and alkaryl;

c. (Surface) is a macromolecular component; and

d. $n \geq 1$.

45. A method of producing an aminimide-functional support comprising the steps of:

reacting a polymer or oligomer containing pendant moieties of OH, NH or SH with a compound of the formula:



wherein

a. R^1 and R^2 each represent alkyl, cycloalkyl, aryl, aralkyl and alkaryl. and R^3 is an amino acid derivative; a nucleotide derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component;

b. coating the reacted polymer or oligomer onto a support to form a film thereon; and

c. heating the coated support to crosslink the film.

46. A method of producing an aminimide-functional support comprising the steps of:

coating a mixture of multifunctional esters and multifunctional epoxides onto a support to form a film thereon; and

reacting the coated support with 1,1'-dialkylhydrazine to crosslink the film.

47. A method of producing an aminimide-functional support comprising the steps of:

coating a mixture of an aminimide-functional vinyl monomer, a difunctional vinyl monomer and a vinyl polymerization initiator onto a support to form a film thereon; and

heating the coating support to form a crosslinked film.

48. An aminimide-functionalized support prepared according to the method of one of claims 45, 46 or 47.

49. A three-dimensional crosslinked random copolymer containing, in copolymerized form:

about 1 to 99 parts of a free-radically polymerizable monomer containing an aminimide group;

up to 98 parts of a free-radically addition-polymerizable comonomer; and

about 1 to 50 parts of at least one crosslinking monomer.

50. The copolymer of claim 49 wherein the comonomer is water-soluble.

51. The copolymer of claim 50 wherein the comonomer is water-insoluble.

52. The copolymer of claim 50 wherein the copolymer is fashioned into a water-insoluble bead, a water-insoluble membrane or a latex particle.

53. The copolymer of claim 50 wherein the copolymer is a swollen aqueous gel suitable for use as an electrophoresis gel.

54. A three-dimensional crosslinked random copolymer that is the reaction product of:

about 1 to 99 parts of a condensation-polymerizable monomer containing a moiety cluster selected from the group consisting of (1) at least three epoxy groups, (2) at least three ester groups, (3) at least one epoxy and at least two ester groups and (4) at least one ester and at least two epoxy groups;

about 1 to 99 parts of a second condensation-polymerizable monomer containing a moiety cluster selected from the group consisting of (1) at least two ester groups, (2) at least two epoxy groups and (3) at least one ester and one epoxy group; and

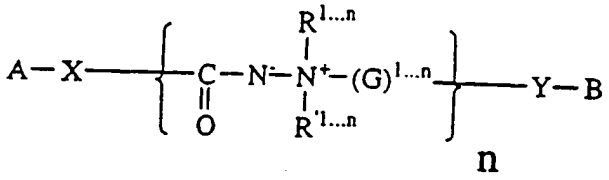
an amount 1,1-dialkylhydrazine equivalent, on a molar basis, substantially equal to the total molar content of epoxy groups.

55. The coploymer of claim 54 wherein the copolymer is fashioned into a water-insoluble bead, a water-insoluble membrane or a latex particle.

56. The copolymer of claim 55 wherein the copolymer is a swollen aqueous gel suitable for use as an electrophoresis gel.

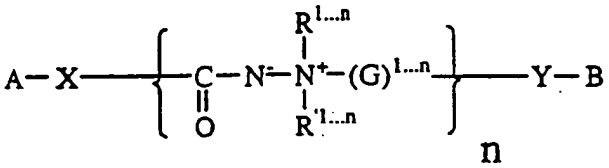
57. A method of making a polymer having a particular water solubility comprising the steps of:

choosing a first monomer having the formula



wherein R and R' are the same or different and are chosen from those organic moieties exhibiting hydrophobicity;

choosing a second monomer having the formula



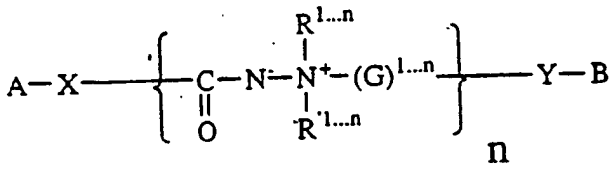
wherein R and R' are the same or different and are chosen from those organic moieties exhibiting hydrophilicity; and

reacting said monomers to provide an effective amount of each monomer in a developing polymer chain until a polymer having the desired water solubility is created.

58. A method according to claim 57 wherein the hydrophobic organic moieties include those which do not have carboxyl, amino or ester functionality.

59. A method according to claim 57 wherein the hydrophilic moieties include those which do not have carboxyl, amino or ester functionality.

60. A method of preparing a synthetic compound to mimic or complement the structure of a biologically active compound or material which comprises synthesizing a compound of the formula:



wherein

A is a chemical bond; hydrogen; an electrophilic group; a nucleophilic group; R'; an amino acid derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component, wherein A and B are optionally connected to each other or to other structures and R is as defined below;

X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

R and R' are the same or different and each is selected from the group consisting of A, B, isomers of A and B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic, aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the

quaternary nitrogen and G may be different in adjacent n units; and

$$n > 1.$$

61. A method according to claim 60 wherein said compound is a pharmacaphore.

62. A method according to claim 60 wherein said compound is a peptide mimetic.

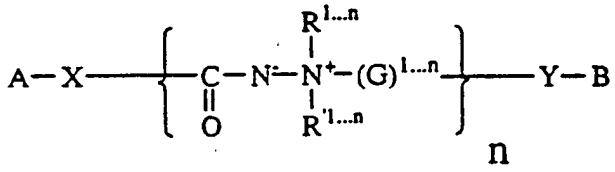
63. A method according to claim 60 wherein said compound is a nucleotide mimetic.

64. A method according to claim 60 wherein said compound is a carbohydrate mimetic.

65. A method according to claim 60 wherein said compound is a reporter compound.

66. A method of preparing a combinatorial library which comprises:

preparing a compound having the formula;



wherein

A is a chemical bond; hydrogen; an electrophilic group; a nucleophilic group; R'; an amino acid derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component,

wherein A and B are optionally connected to each other or to other structures and R is as defined below;

X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

R and R' are the same or different and each is selected from the group consisting of A, B, isomers of A and B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic, aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

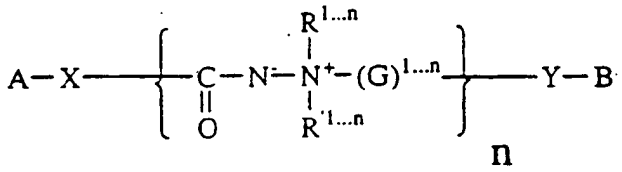
G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

$n \geq 1$; and

conducting further reactions with the compound to form a combinatorial library.

67. A method of separating a desired compound from a plurality of compounds, which comprises;

preparing a separator compound having the formula:



wherein

A is a chemical bond: hydrogen; an electrophilic group; a nucleophilic group; R'; an amino acid derivative; a carbohydrate derivative; an organic structural motif; a reporter element; an organic moiety containing a polymerizable group; or a macromolecular component, wherein A and B are optionally connected to each other or to other structures and R is as defined below;

X and Y are the same or different and each represents a chemical bond or one or more atoms of carbon, nitrogen, sulfur, oxygen or combinations thereof;

R and R' are the same or different and each is selected from the group consisting of A, B, isomers of A and B, cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic, aryl and substituted or heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

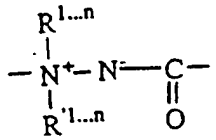
G is a chemical bond or a connecting group that includes a terminal carbon atom for attachment to the quaternary nitrogen and G may be different in adjacent n units; and

$n \geq 1$; and

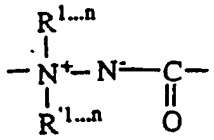
contacting the separator compound with the plurality of compounds; and

differentiating the second compound from plurality of compounds.

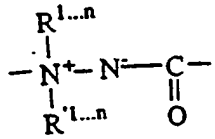
68. The method of claim 57 or 60 wherein G is an aminimide isomer having the formula;



69. The composition of claims 1, 10, 11, 13, 15, 17, 20, 22 or 26 wherein G is an aminimide isomer having the formula;



70. The process of claim 33 or 36 wherein G is an aminimide isomer having the formula;



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12612

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C09B 44/00; C07C 245/00
US CL :564/148, 149, 150, 151; 534/574, 886; 530/324, 350, 412, 413
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. CL : 564/148, 149, 150, 151; 534/574, 886; 530/324, 350, 412, 413, 322, 399; 436/71; 525/77, 83; 424/78

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Proc. Natl. Acad. Sci. Volume 89, issued October 1992, Reyna J. Simon et al. "Peptoids: A modular approach to drug discovery", pages 9367-9371.	1-44, 60-65
A	Chemical Abstracts, Volume 105, No. 19, issued 1986, Moulton et al. "Studies on the transverse tubule membrane magnesium ATPase. Lectin-induced alterations of kenetic behavior", abstract no. 167889v.	11-12
A	The FASEB Journal, Volume 7, issued April 1993, Stanley T. Crooke "Progress toward oligonucleotide therapeutics: Pharmacodynamic properties", pages 533-539.	11-12

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
07 JUNE 1994

Date of mailing of the international search report
JUN 17 1994

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12612

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Volume 120, No. 15, issued 1993, Toyokuni et al., "Multivalent mimetics and peptide mimetics for blocking carbohydrate-dependent cellular interaction and for eliciting anti-carbohydrate T-Cell response", abstract no. 183041c.	1-14, 17-19
A	Chemical Abstracts, Volume 111, no. 5, issued 31 July 1989, Ghosh et al., "Synthesis of 5'-oligonucleotide hydrazide derivatives and their use in preparation of enzyme-nucleic acid hybridization probes", abstract no. 36183m.	13-14, 17-19
A	Chemical Abstracts Volume 115, no. 11, issued 16 September 1991, Wrasidlo, "Interfacial condensation of bioactive compounds and site specific compounds such as monoclonal antibodies and conjugates thereof", abstract no. 112642k.	15-16
A	Chemical Abstracts, Volume 105, no. 6, issued 11 August 1986, Kroschwitz, "Aminimide polymers", abstract no. 43373e.	20-25
A	Chemical Abstracts, Volume 89, no. 14, issued 1989, Miron et al., "Unsaturated aminimide for anaerobic hardening", abstract no. 111205c.	20-25, 43-44
A	Chemical Abstracts, Volume 93, no. 6, issued 1980, Kuwamura, "Surface -Active Agents and Detergents" abstract no. 48,980s.	1-44, 60-65
A	Chemical Abstracts, Volume 108, no. 28, issued 1988, Inokuma, "Surface active crwon ethers, XI, Synthesis and properties of aminimides and their crown derivatives bearing an L-alinine residue, "abstract no. 223506u.	1-44, 60-65
A	US, A, 4,012,364 (FARBER) 15 March 1977.	20-21, 43-44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12612

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims drawn to the following distinct inventions:

I. Claim 10, drawn to a peptide mimetic, classified in class 530, subclass 300+ depending on the specific peptide.

II. Claims 11-12, drawn to a nucleotide mimetic, classified in class 536, subclass 27, for example.

III. Claims 13-14, drawn to a carbohydrate mimetic, classified in class 536, subclass 1.11+.

IV. Claims 15-16, drawn to a pharmaceutical compound containing an organic structural motif, classified in class 514, subclass 1+ depending on the particular structure.

V. Claims 17-19, drawn to a reporter compound, classified in class 552, subclass depending on the structure of the reporter component.

VI. Claims 20-21, drawn to a polymer, classified in classes 520-528, various subclasses depending on the polymerizable groups.

VII. Claims 22-25, drawn to a substrate, classified in class 424, subclass 484+ depending upon the desired substrate.

VIII. Claims 26-40, drawn to a chiral composition of matter and a method of synthesizing the same, classified in class 530, various subclasses depending on the composition of matter, for example.

IX. Claims 41-42, drawn to a lipid mimetic composition, classified in class 436, subclass 71.

X. Claims 43-44, drawn to a functional polymer, classified in classes 525-528, subclass varies depending on the particular surface.

XI. Claims 45-48, drawn to a method of producing an aminimide-functional support and the product obtained thereby, classified in class 428, subclass 411.1+.

XII. Claims 49-56, drawn to a three-dimensional crosslinked random copolymer, classified in class 424, subclass 78+.

XIII. Claims 57-59, drawn to a method of making a polymer having a particular water solubility, classified in class 424, subclass 78+.

XIV. Claims 66-70, drawn to a method of preparing a combinatorial library and a method of separating a desired compound from a plurality of compounds, classified in various class and subclasses depending on the compound.

Note that claims 1-9 and 60-65 are linking claims, linking to claims 10 to 44.